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(54) Title: 2-CYCLOHEXYL BENZIMIDAZOLE NMDA/NR2B ANTAGONISTS

(57) Abstract: Novel 4-substituted cyclohexanes substituted in the 1-position with 2-benzimidazoles, 2-imidazopyridines, or 4-imidazoles either directly or through a C_1-C_4alkyl, cycloalkyl, hydroxyalkyl, alkoxy or aminoalkyl chain are effective as NMDA NR2B antagonists useful for relieving pain.

TITLE OF THE INVENTION

2-CYCLOHEXYL BENZIMIDAZOLE NMDA/NR2B ANTAGONISTS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel 2-cyclohexyl benzimidazoles. In particular, this invention relates to novel 4-substituted cyclohexanes substituted in the 1-position with 2-benzimidazoles, 2-imidazopyridines, or 4-imidazoles either directly or through a C_1-C_4alkyl, cycloalkyl, hydroxyalkyl, alkoxy or aminoalkyl chain that are effective as NMDA NR2B antagonists useful for relieving pain.

Ions such as glutamate play a key role in processes related to chronic pain and pain-associated neurotoxicity – primarily by acting through N-methyl-D-aspartate ("NMDA") receptors. Thus, inhibition of such action – by employing ion channel antagonists, particularly NMDA antagonists – can be beneficial in the treatment and control of pain.

Known NMDA antagonists include ketamine, dextromorphan, and 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid ("CPP"). Although these compounds have been reported (J.D.Kristensen, et al., *Pain*, 51:249-253 (1992); K.Eide, et al., *Pain*, 61:221-228 (1995); D.J.Knox, et al., *Anaesth. Intensive Care* 23:620-622 (1995); and M.B.Max, et al., *Clin. Neuropharmacol.* 18:360-368 (1995)) to produce symptomatic relief in a number of neuropathies including postherpetic neuralgia, central pain from spinal cord injury, and phantom limb pain, widespread use of these compounds is precluded by their undesirable side effects. Such side effects at analgesic doses include psychotomimetic effects such as dizziness, headache, hallucinations, dysphoria, and disturbances of cognitive and motor function. Additionally, more severe hallucinations, sedation, and ataxia are produced at doses only marginally higher than analgesic doses. Thus, it would be desirable to provide novel NMDA antagonists that are absent of undesirable side effects or that produce fewer and/or milder side effects.

NMDA receptors are heteromeric assemblies of subunits, of which two major subunit families designated NR1 and NR2 have been cloned. Without being

bound by theory, it is generally believed that the various functional NMDA receptors in the mammalian central nervous system ("CNS") are only formed by combinations of NR1 and NR2 subunits, which respectively express glycine and glutamate recognition sites. The NR2 subunit family is in turn divided into four individual subunit types: NR2A, NR2B, NR2C, and NR2D. I.Ishii, et al., *J. Biol. Chem.*, 268:2836-2843 (1993), A.Wenel, et al., *Neural Report*, 7:45-48 (1995), and D.J.Laurie et al., *Mol. Brain Res.*, 51:23-32 (1997) describe how the various resulting combinations produce a variety of NMDA receptors differing in physiological and pharmacological properties such as ion gating properties, magnesium sensitivity, pharmacological profile, as well as in anatomical distribution.

For example, while NR1 is found throughout the brain, NR2 subunits are differentially distributed. In particular, it is believed that the distribution map for NR2B lowers the probability of side effects while producing pain relief. For example, S.Boyce, et al., *Neuropharmacology*, 38:611-623(1999) describes the effect of selective NMDA NR2B antagonists on pain with reduced side-effects. Thus, it would be desirable to provide novel NMDA antagonists that target the NR2B receptor.

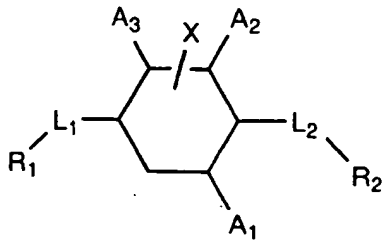
International Patent Publication WO94/21615 describes benzimidazole-piperidine compounds utilized as dopamine D4 antagonists. Phenol compounds described as NMDA antagonists are described in U.S. Patent Nos. 5,306,723 and 5,436,255, and in International Patent Publications WO91/17156, WO92/19502, WO93/02052, WO94/29571, WO95/28057, WO96/37226, and EP 04422506. Benzyl piperidines substituted with phenols or imidazoles are described in Z.-L.Zhou, et al., *J. Medicinal Chemistry*, 42:2993-3000(1999); T.F.Gregory, et al., Poster #94, 218th National Meeting American Chemical Society, New Orleans, Louisiana, August 22-26, 1999. Other NMDA NR2B selective compounds are described in European Patent Publication EP 787493 and *British J. Pharmacol.*, 123:463(1998). However, there continues to be a need for novel NMDA antagonists that target the NR2B receptor.

SUMMARY OF THE INVENTION

The present invention relates to novel 2-cyclohexyl benzimidazoles. The present invention also forms novel pharmaceutical compositions utilizing these novel compounds. Further, this invention includes novel methods to treat pain by utilizing the novel compounds.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the compounds of this invention are represented by Formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R_1 is 2-benzimidazole, 2-imidazopyridine, or 2-quinazoline; optionally substituted with fluoro, amino, or hydroxy;

R_2 is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_1 and L_2 are independently C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, amino, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

A_1, A_2, and A_3 are each hydrogen or i) A_1 and A_2 form a two carbon bridge or ii) A_1 and A_3 form a two carbon bridge; and
optionally substituted with X, wherein X is hydroxy, amino, C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

In an embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

R_1 is 2-benzimidazole;

R_2 is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_1 and L_2 are independently C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, amino, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

A_1, A_2, and A_3 are each hydrogen or i) A_1 and A_2 form a two carbon bridge or ii) A_1 and A_3 form a two carbon bridge; and

optionally substituted with X, wherein X is hydroxy, amino, C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

Unless otherwise stated, the terms "carbonyl" and "aminocarbonyl" include short C_1-C_2 termini. The terms include, for example, -CO-, -CONH-, $-CH_2CO-$, $-CH_2CONH-$, $-C_2H_4CO-$, $-C_2H_4CONH-$, $-COCH_2-$, $-CONHCH_2-$, $-COC_2H_4-$, $-CONHC_2H_4-$, $-CH_2COCH_2-$, $-CH_2CONHCH_2-$, $-CH_2COC_2H_4-$, $-CH_2CONHC_2H_4-$, $-C_2H_4COC_2H_4-$, and $-C_2H_4CONHC_2H_4-$. Similarly, unless otherwise stated, the term "aminoC_1-C_4alkyl" includes short C_1-C_2 termini. The term includes, for example, $-CH_2NH-$, $-C_2H_4NH-$, $-C_3H_6NH-$, $-C_4H_8NH-$, $-CH_2NHCH_2-$, $-C_2H_4NHCH_2-$, $-C_3H_6NHCH_2-$, $-C_4H_8NHCH_2-$, $-CH_2NHC_2H_4-$, $-C_2H_4NHC_2H_4-$, $-C_3H_6NHC_2H_4-$, $-C_4H_8NHC_2H_4-$, $-NHCH_2-$, $-NHC_2H_4-$, $-NHC_3H_6-$, $-NHC_4H_8-$, $-CH_2NHC_2H_4-$, $-CH_2NHC_3H_6-$, $-CH_2NHC_4H_8-$, $-C_2H_4NHC_3H_6-$, and $-C_2H_4NHC_4H_8-$.

Unless otherwise stated, the term "carbamate" is used to include $-OCOOC_1$-C_4alkyl, $-NHCOOC_1$-C_4alkyl, and $-OCONHC_1$-C_4alkyl.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "SEM" is used to describe $-CH_2-O-CH_2CH_2-Si(CH_3)_3$.

The term "C_0" means that the carbon is not present. Thus, "C_0-C_5" means that there are from none to five carbons present – that is, five, four, three, two, one, or no carbons present. Accordingly, "C_0-C_5alkyl" means a direct bond for the case of "C_0".

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-

ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled

release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 1mg to about 500mg of the active ingredient and each

cachet or capsule preferably containing from about 1 to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or

more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Experimental Protocols

Assessing the Activity of Selected Compounds to Inhibit NR1A/2B NMDA Receptor Activation (FLIPR Assay)

The activity of selected compounds to inhibit NR1A/2B NMDA receptor activation measured as NR1A/2B receptor-mediated Ca^{2+} influx is assessed by the following procedure:

NR1A/2B receptor transfected L(tk) cells are plated in 96-well format at 3 x 10^6 cells per plate and grown for one - two days in normal growth media (Dulbeccos MEM with Na pyruvate, 4500 mgglucose, pen/strep, glutamine, 10% FCS and 0.5mg/ml geneticin). NR1A/2B-expression in these cells is induced by the addition of 4nM dexamethasone in the presence of 500μM ketamine for 16 - 24 hours. After receptor induction cells are washed using a Labsystem Cellwasher two times with assay buffer (Hanks balanced salt solution (HBSS-Mg^{++} free) containing 20mM HEPES, 0.1% BSA, 2mM $CaCl_2$ and 250μM probenecid). The cells of each 96 well cell plate are loaded with the Ca^{++} sensitive dye Fluo-3 (Molecular Probes, Inc.) at 4μM in assay buffer containing 0.5% FBS, and 0.04% pluronic F-127 (Molecular Probes, Inc.) for 1h at 37 °C avoiding light. The cells are then washed with the Cellwasher four times with assay buffer leaving them in 100μl buffer. Test compounds in solution are pipetted by FLIPR (Fluorometric Imaging Plate Reader) into each test well for a 2min pretreatment. During this time the fluorescence intensity is recorded (excitation at 488nm and emission at 530nm). The glutamate/glycine 50μl agonist solution (final concentration 1μM/1μM) is then added by FLIPR into each well already containing 150μl of buffer (containing the test compound or vehicle) and the fluorescence is continuously monitored for 10min. The endpoint fluorescence values are used to determine an IC_{50} value comparing the

agonist-stimulated signal for the vehicle alone sample and that for the cells incubated with each concentration of test compound.

Determining the Apparent Dissociation Constant (Ki) of Compounds for Human NR1A/NR2B Receptors (Binding Assay):

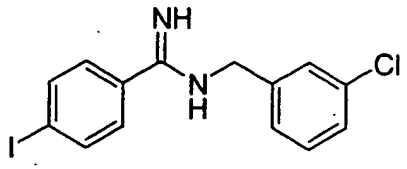
The radioligand binding assay is performed at room temperature in 96-well microtiter plates with a final assay volume of 1.0mL in 20mM Hepes buffer (pH 7.4) containing 150mM NaCl. Solutions of test compounds were prepared in DMSO and serially diluted with DMSO to yield 20µL of each of 10 solutions differing by 3-fold in concentration. Non-specific binding (NSB) using hot AMD-1 (10µM final concentration) and total binding (TB) by using DMSO (2% final concentration). A solution of NR1A/NR2B receptors (40pM final concentration) and tritiated AMD-2 (1nM final concentration) were added to the test compounds. After 3h of incubation at room temperature, samples are filtered through Packard GF/B filters (presoaked in 0.05% PEI, polyethyleninine Sigma P-3143) and washed 10 times with 1mL of cold 20mM Hepes buffer per wash. After vacuum drying of the filter plates, 40µL of Packard Microscint-20 was added and bound radioactivity determined in a Packard TopCount. The apparent dissociation constant (Ki), the maximum percentage inhibition ($\%I_{max}$), the minimum percentage inhibition ($\%I_{min}$) and the hill slope (nH) were determined by a non-linear least squares fitting the bound CPM data to Equation #1 below.

Equation#1:

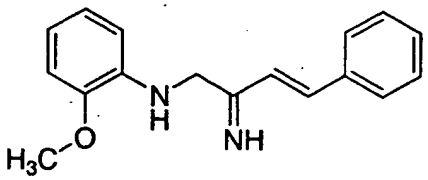
$$\text{CPM Bound} = \frac{(SB)(\%I_{max} - \%I_{min})}{(1 + ([Drug] / (Ki\ [L\text{-}844,345]/K_D))^{nH})} + NSB + (SB)(1 - \%I_{max})$$

where, K_D is the apparent dissociation constant for the radioligand for the receptor as determined by hot saturation and SB is the specifically bound CPM determined from the difference of TB and NSB.

AMD-1

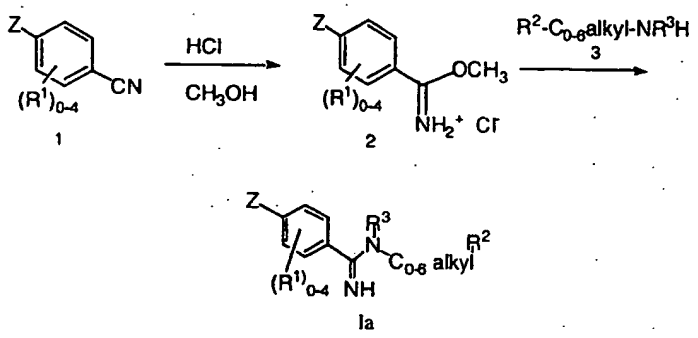


AMD-2



Compounds AMD-1 and AMD-2 can be synthesized in accordance with the following general reaction schemes.

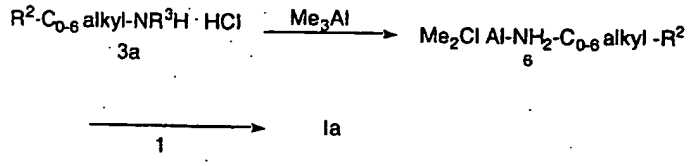
SCHEME 1



In accordance with scheme 1, hydrogen chloride is bubbled through a solution of the appropriately substituted benzonitrile 1 in methanol at room temperature. The volatiles are removed under reduced pressure and the resulting residue is triturated with ether and filtered to yield the desired imidate 2. Imidate 2 is dissolved in methanol at ambient temperature, treated with amine 3 at ambient temperature and stirred under argon. The volatiles are removed under reduced

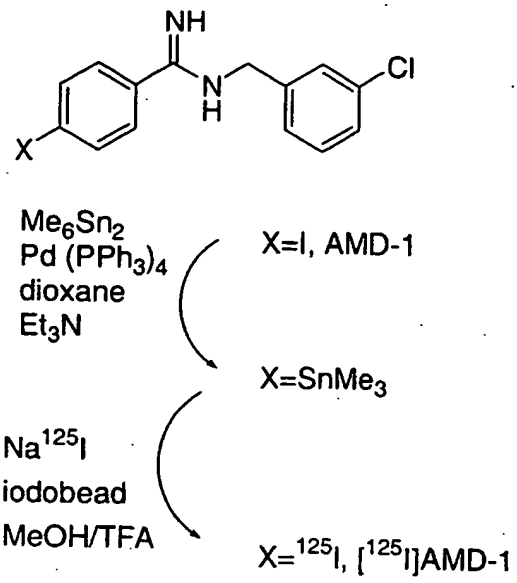
pressure and the residue purified by preparative HPLC or trituration with ether to afford amidine Ia.

SCHEME 2



In accordance with scheme 2, at room temperature under argon, amine 3a is dissolved in ether and was treated with 1-M hydrogen chloride in ether (1 equiv.) in a single portion. The resulting precipitate is stirred vigorously for 10 minutes. The volatiles are removed under reduced pressure. The residue is suspended in toluene, cooled to 0°C under argon, treated with 2.0-M trimethylaluminum (1.05 equiv.) in a dropwise manner, and stirred for 45 minutes at room temperature to afford intermediate 6 (not isolated). Compound 6 is added to a solution of nitrile 1 in toluene. The reaction is heated to 80°C without stirring in a sealed tube for 18h, cooled to ambient temperature, poured onto a silica gel column and eluted with methanol/dichloromethane to give the amidine 4.

Preparation of [^{125}I]AMD-1



Tritiated AMD-1 was prepared by the following procedure: A mixture of AMD-1, hydrochloride salt, (5mg, 0.012mmol) in dioxane (0.2mL) containing triethylamine (4μL) was treated with hexamethylditin (5μL), a catalytic amount of palladium catalyst and heated at 100°C for 45 minutes. The reaction was cooled to room temperature, filtered through a glass wool plug, rinsed with methanol and concentrated *in vacuo* to give 10.7mg of a brown oil. The oil was dissolved in methylene chloride and passed through a small silica column eluting with methylene chloride followed by 5% methanol/methylene chloride. Fractions containing the trimethylstannane (Rf 0.26 in 10% methanol/methylene chloride) were pooled and concentrated *in vacuo* to give 4.5mg of the trimethylstannane as a clear colorless oil. This material was further purified by HPLC (C18 Econosil, 10x250mm, 20 minute linear gradient, 30% MeCN:70% H_2O (0.1% TFA) to 90% MeCN, 3mL/min, 254nm, retention time 15 minutes) to give 3mg of the trimethylstannane.

A $Na^{125}I$ shipping vial (10mCi, Amersham) was charged with a stir bar, an iodobead, 50μL of methanol and stirred five minutes at room temperature. A solution of the trimethylstannane (0.1mg) in 50μL of methanol containing 5μL of trifluoroacetic acid was added and the reaction was stirred for five minutes. The reaction was quenched with 50μL of ammonium hydroxide and purified by HPLC (C18 Vydac protein and peptide column, 4.6 x 250 mm, 20 minute linear gradient,

30% MeCN:70% H_2O (0.1% TFA) to 90% MeCN, 1mL/min, retention time 11minutes). Fractions containing the radioactive product were pooled and concentrated *in vacuo* to give 989μCi of [^{125}I]AMD-1 with a specific activity of 898Ci/mmol as measured by UV absorbance at 272nm.

Synthesis of Tritiated AMD-2

Tritiated AMD-2 was prepared by the following procedure: The phenol of AMD-2 (2mg; 0.008mmol) dissolved in dimethylformamide (0.6mL) and potasium carbonate (1.2mg) for 1hr. High specific activity tritiated methyl iodide (50mCi, 0.0006mmol, in toluene 1mL, American Radiolabeled Chemicals) was added at room temperature and stirred for 2 hours. The reaction mixture was filtered using a Whatman PTFE 0.45μm syringeless filter device to remove any insoluable potassium carbonate, washed with Abs. ethanol (2mL, Pharmco), and the combined filtrates were concentrated to dryness at room temperature using a rotary evaporator; this also removed any unreacted tritiated methyl iodide. The residue was purified by HPLC chromatography on a Phenomenx Luna C8 semi-prep column (Luna 5 micro C8(2), 250x10.0 mm) using a gradient system of 20/80 acetonitrile/water with 0.1% trifluoroacetic acid to 100% acetronitrile with 0.1% trifluoroacetic acid in 20min. Total activity of the product was 8mCi. Further purification was effected by absorption onto a Waters C-18 Sep-pak column (Waters Sep-Pak PLUS C18) and elution with water followed by absolute ethanol. The product was diluted with absolute ethanol (10mL) before submission for final analysis.

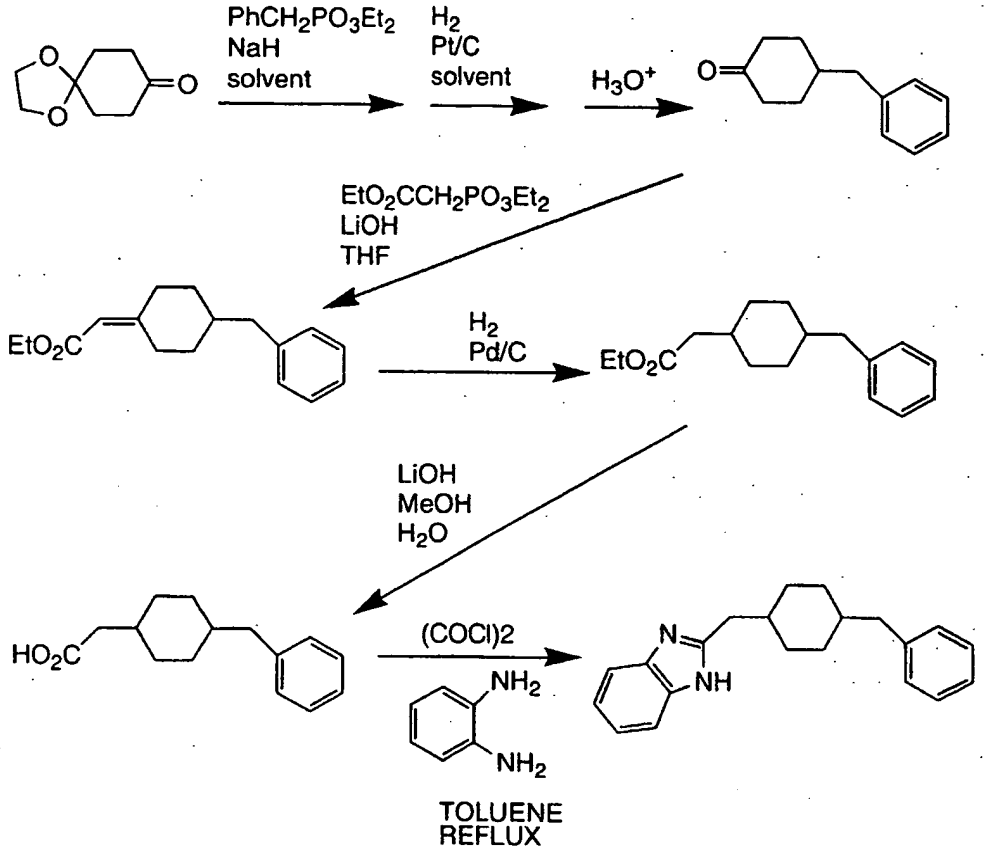
The compounds of this invention exhibit less than 50μM in the FLIBR and binding assays. Thus, the compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as NMDA NR2B antagonists. Accordingly, another aspect of the invention is the treatment of pain, migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke – maladies that are amenable to amelioration through inhibition of NMDA NR2B receptors – by the administration of an effective amount of the compounds of this invention.

The following examples are provided to more fully illustrate the present invention, and are not to be construed as limiting the scope of the claims in any manner.

EXAMPLES

The compounds of this invention can be prepared according to Scheme 1 shown below:

Scheme 1



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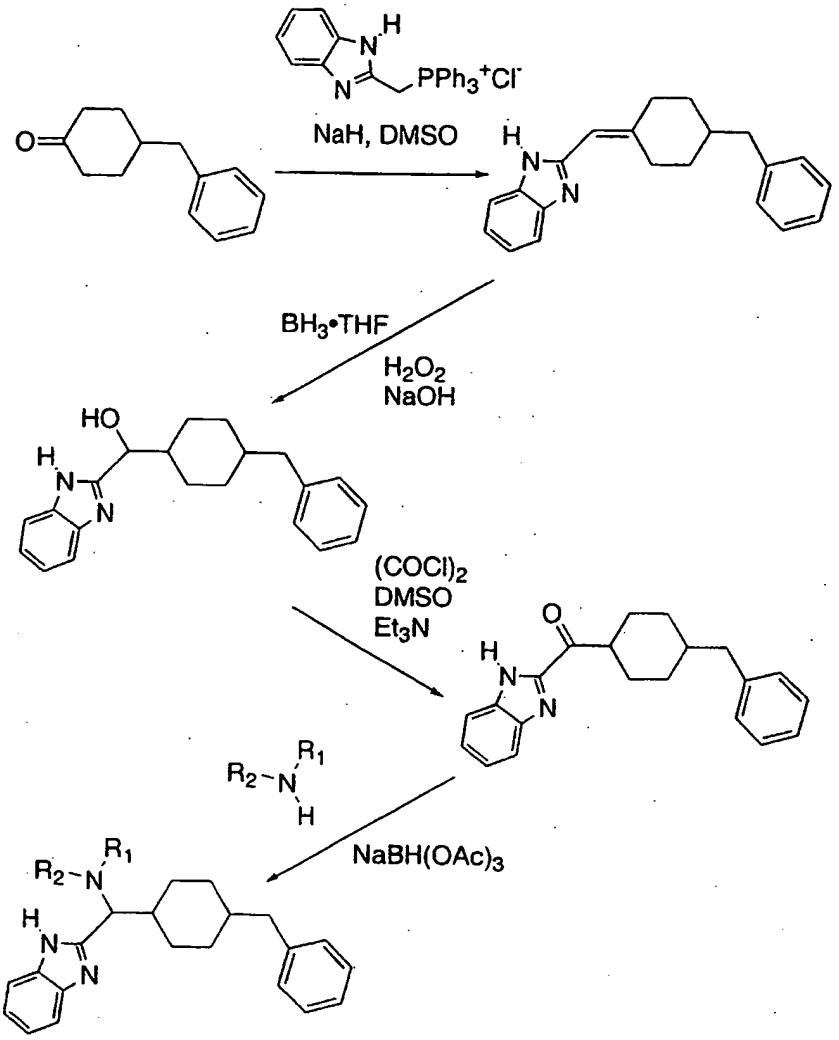
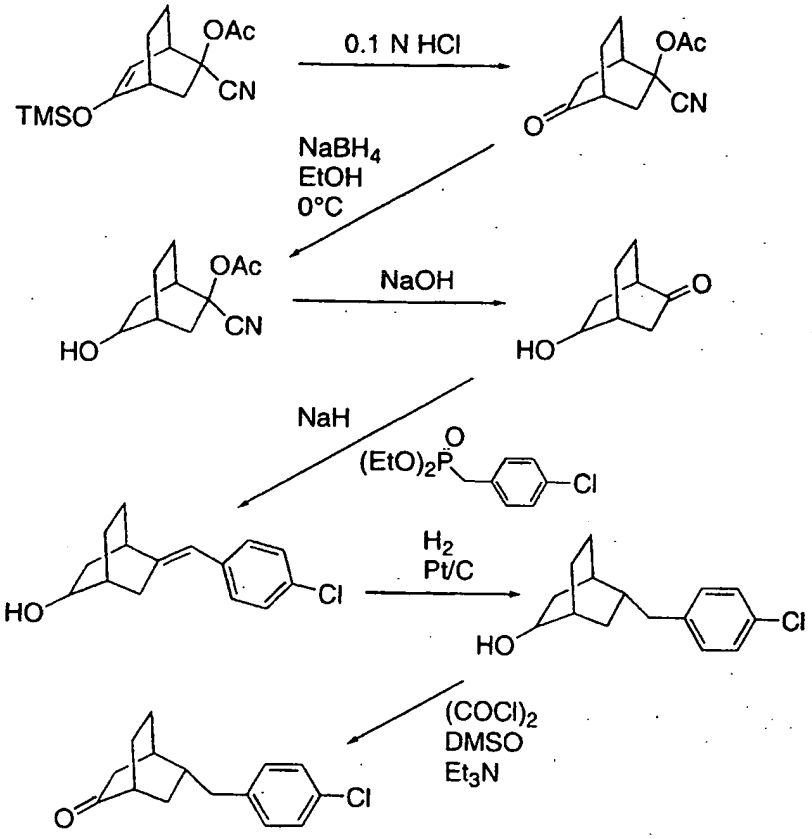
The compounds of this invention can be prepared according to Scheme 2 shown below:

Scheme 2



The compounds of this invention can be prepared according to Scheme 3 shown below:

Scheme 3



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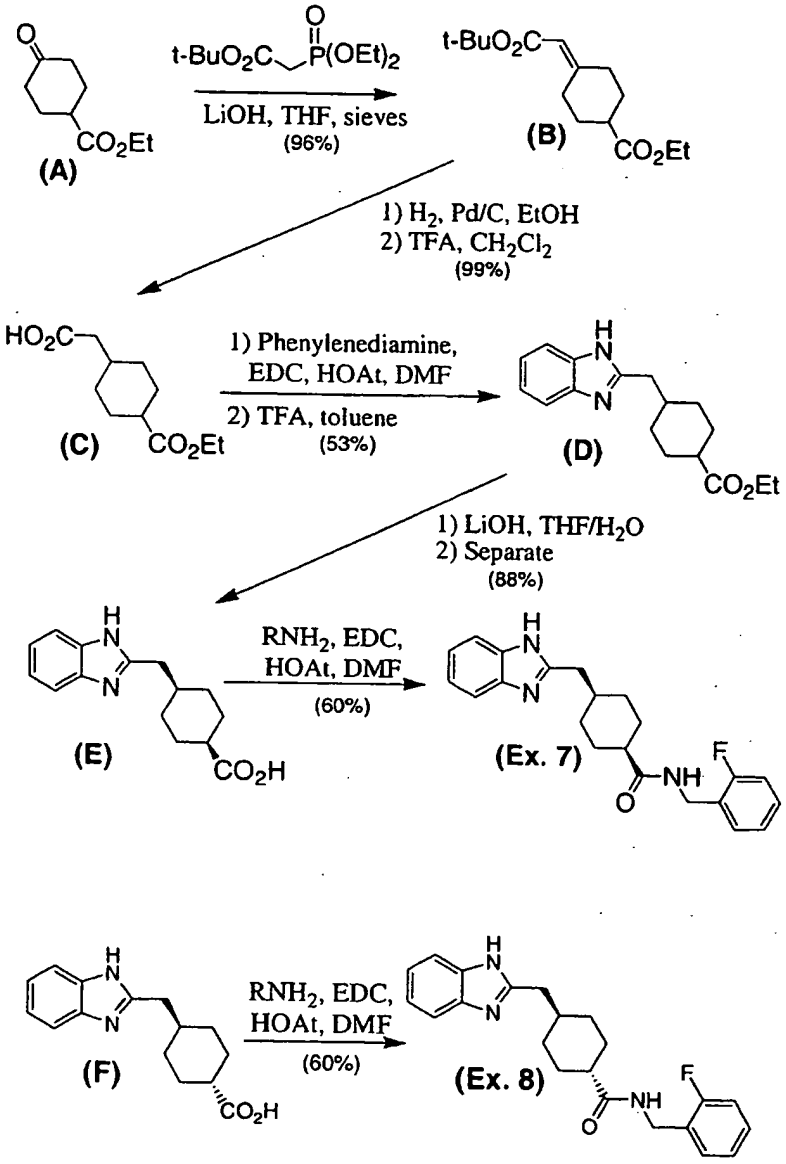
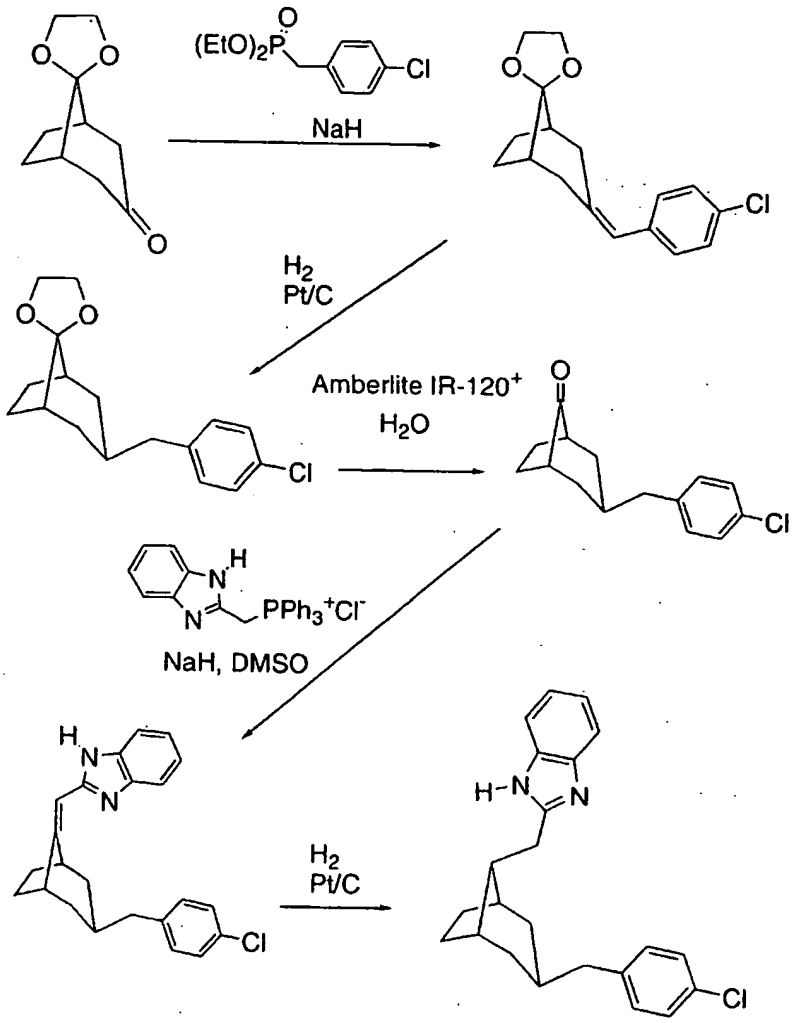
The compounds of this invention can be prepared according to Scheme 4 shown below:

Scheme 4



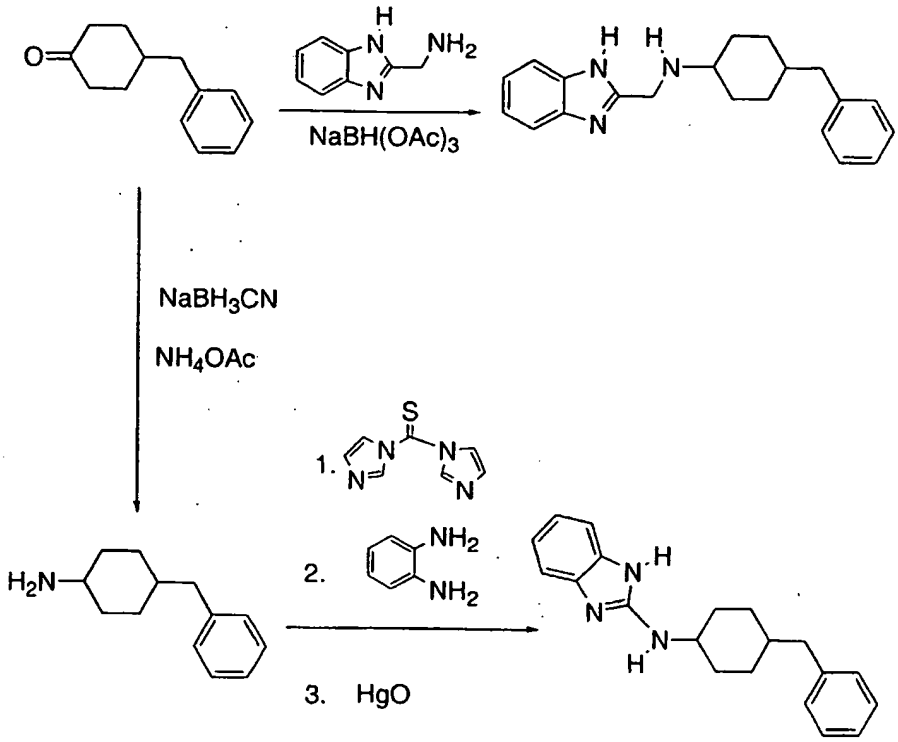
The compounds of this invention can be prepared according to Scheme 5 shown below:

Scheme 5

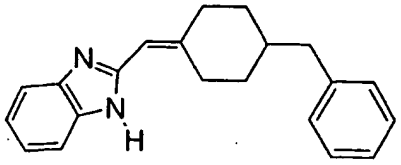


The compounds of this invention can be prepared according to Scheme 6 shown below:

Scheme 6



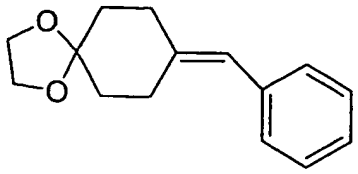
EXAMPLE 1



2-(4-Benzyl-cyclohexylidenemethyl)-1H-benzimidazole

Example 1 was prepared by the following procedure.

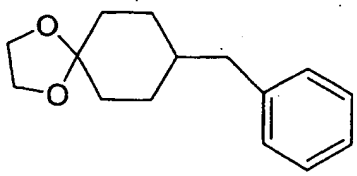
Step 1:



8-Benzylidene-1,4-dioxa-spiro[4.5]decane:

To a stirred solution of 20g of 1,4-dioxa-spiro[4.5]decan-8-one and 35g of diethyl benzylphosphonate in 60mL of 1,3-dimethyl-2-imidazolidinone dried over 4Å mol sieves was added 7g of 60% NaH oil dispersion. The mixture was allowed to stir overnight, diluted with 500mL of water and extracted with 3X100mL of ether. Combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 5:95 ethyl acetate:hexane to 1:3 ethyl acetate:hexane gave 28g of olefin as a colorless oil.

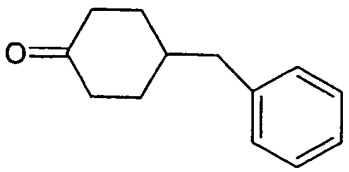
Step 2:



8-Benzyl-1,4-dioxa-spiro[4.5]decane:

A solution of 28g of 8-benzylidene-1,4-dioxa-spiro[4.5]decane and 1g of 5% palladium on carbon in 250mL of ethanol was allowed to stir overnight under 1atm of hydrogen. The catalyst was filtered off and the solution concentrated to give 28g of 8-benzyl-1,4-dioxa-spiro[4.5]decane as an oil.

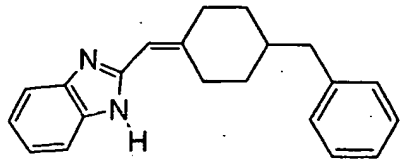
Step 3:



4-Benzyl-cyclohexanone:

A mixture of 28g of 8-benzyl-1,4-dioxa-spiro[4.5]decane, 100mL of water, 10mL of methanol and 20g of Amberlite™ IR-120$^+$ was heated to reflux for 5h. After cooling, removal of solvents under reduced pressure gave 24g of 4-benzyl-cyclohexanone as an oil.

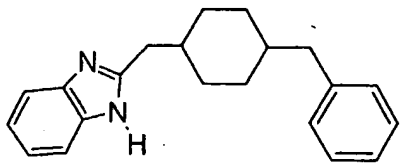
Step 5:



2-(4-Benzyl-cyclohexylidenemethyl)-1H-benzimidazole:

A stirred solution of 0.5g of 4-benzyl-cyclohexanone, 1.0g of 2-benzimidazolylmethyltriphenylphosphonium chloride and 15mL of anhydrous DMSO was heated gently until a clear solution was obtained, then cooled to room temperature. To this solution was added 90mg of 60% sodium hydride oil dispersion. The resulting orange solution was stirred for 48h at room temperature, then quenched with 200mL of water and extracted into 3X50mL portions of ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated. Purification by preparative TLC eluting with 25% ethyl acetate in hexane gave 220mg of a white solid: MS (m+1) = 303.4; ^{1}H NMR (400MHz, $CDCl_3$) 7.5 (m, 2H), 7.2-7.0 (3 x m, 7H), 6.2 (s, 1H), 3.75 (d, 1H), 2.45 (dd, 2H), 2.3 (d, 1H), 2.2 (t, 1 H), 2.05 (m, 1H), 1.8 (m, 4H), 1.05 (m, 2H).

EXAMPLE 2

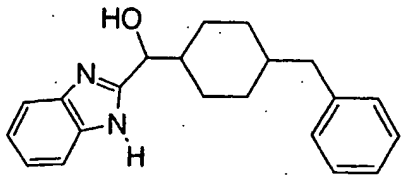


2-(4-Benzyl-cyclohexylmethyl)-1H-benzimidazole:

Hydrogenation of 0.10g of 2-(4-benzyl-cyclohexylidenemethyl)-1H-benzimidazole over 0.05g of 5% platinum on carbon in 10mL of ethanol at 1atm overnight gave 0.1g of 2-(4-benzyl-cyclohexylmethyl)-1H-benoimidazole as a 2:1 mixture of cis and trans isomers. Chromatography on a Chiralpak™ column eluting with a gradient of 70:30 to 30:70 hexane and 2-propanol gave 2-(4-benzyl-cyclohexylmethyl)-1H-benoimidazole: RT = ??????min; MS (m+1) =; ^{1}H NMR (400MHz, $CDCl_3$)

Later fractions yielded 2-(4-benzyl-cyclohexylmethyl)-1H-benoimidazole; MS (m+1) =; ^{1}H NMR (400MHz, $CDCl_3$)

EXAMPLE 3

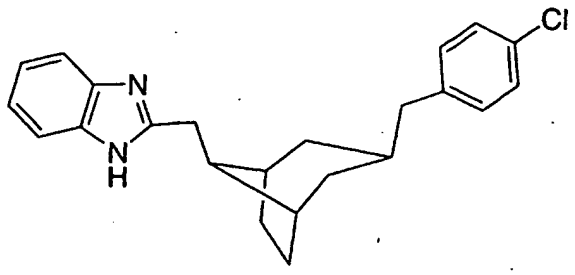


(1H-Benzoimidazol-2-yl)-(4-benzyl-cyclohexyl)-methanol:

Example 3 was prepared by the following procedure. To a stirred solution of 20mg of 2-(4-benzyl-cyclohexylidenemethyl)-1H-benzimidazole in 10mL of THF cooled in an ice bath was added 1mL of 1M borane • THF. After stirring for 24h warming to room temperature, 0.5mL of water was added followed by 0.5mL of 6N sodium hydroxide and 0.5mL of 30% hydrogen peroxide. After 30min, the solution was diluted with 100mL of chloroform, washed 2X10mL of water, dried over magnesium sulfate and concentrated to dryness.

Preparative thin-layer chromatography eluting with 25% ethyl acetate in hexane gave 11mg of (±)- cis and trans (1H-benzimidazol-2-yl)-(4- benzyl-cyclohexyl)-methanol as a gummy resin: MS (m+1) = 321.4; ^{1}H NMR (400MHz, $CDCl_3$) 7.6 (m, 2H), 7.2 (m, 7H), 4.85 and 4.8 (2 x d, 1H), 2.6 and 2.42 (2 x d, 2H).

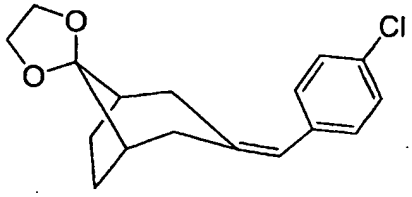
EXAMPLE 4



2-[3-(4-Chloro-benzyl)-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole

Example 4 was prepared by the following procedure.

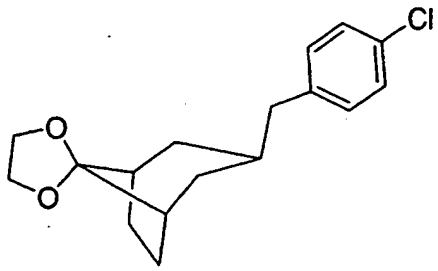
Step 1:



Ethylene ketal of 3-(4-chloro-benzylidene)-bicyclo[3.2.1]octan-8-one:

To a stirred solution of 1g of 3-mono-ethylene ketal of bicyclo[3.2.1]octane-3,8-dione (prepared by Jones oxidation of the mono-ethylene ketal of 3-endo-hydroxy-bicyclo[3.2.1]octan-8-one which was prepared by the procedure described by M. Povarny, P. Schreiber, G. Kraiss and K. Nador, *Tetrahedron Letters*, 25:1311-12(1984) and 2.4 g of diethyl 4-chlorobenzylphosphonate in 5mL of 1,3-dimethyl-2-imidazolidinone dried over 4Å mol sieves was added 0.30g of 60% NaH oil dispersion. The mixture was allowed to stir overnight, diluted with 200mL of water and extracted with 3X100mL of ethyl acetate. Combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Low pressure chromatography over silica gel eluting with a gradient of 5:95 ethyl acetate:hexane to 1:3 ethyl acetate:hexane gave 1.9g of the ethylene ketal of 3-(4-chloro-benzylidene)-bicyclo[3.2.1]octan-8-one as a colorless oil.

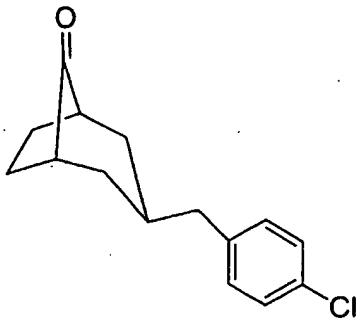
Step 2:



Ethylene ketal of 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one:

Hydrogenation of 1.9g of the ethylene ketal of 3-(4-chloro-benzylidene)-bicyclo[3.2.1]octan-8-one over 0.4g of 5% platinum on carbon in 50mL of ethanol under 1atm of hydrogen for 3h gave 1.9g the ethylene ketal of 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one as a thick oil: ^{1}H NMR (400MHz, $CDCl_3$): The crude product was a 3:1 mixture of exo:endo by peak integration of the exo benzylic protons at 2.45 (d):endo benzylic protons at 2.78 (d).

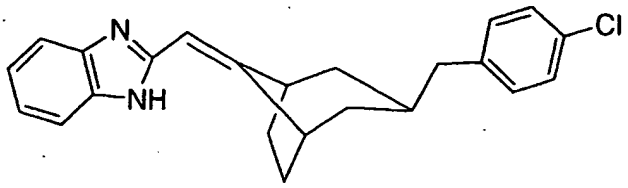
Step 3:



3-(4-Chloro-benzyl)-bicyclo[3.2.1]octan-8-one:

A stirred mixture of 1.9g of the ethylene ketal of 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one, 10mL of dioxane, 50mL of water and 5g of Amberlite™ IR-120+ was heated to reflux for 8h, cooled, filtered and extracted into 5X50mL of ether. Combined extracts were dried over magnesium sulfate and concentrated. The crude 3:1 mixture of exo and endo 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one, 1.3g, was an oil.

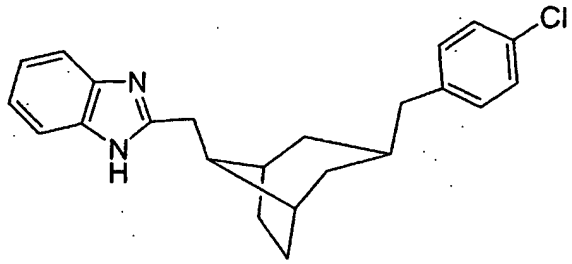
Step 4:



2-[3-(4-Chloro-benzyl)-bicyclo[3.2.1]oct-8-ylidenemethyl]-1H-benzimidazole:

To a stirred solution of 0.25g of 2-benzimidazolylmethyl triphenyl phosphonium chloride and 0.1g of 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one in 5mL of DMSO (heat to dissolve) at room temperature was added 60mg of sodium hydride 60% oil dispersion. After the orange-red mixture was stirred for 24h, conversion was complete and the solution was diluted with 100mL of water and extracted into 3X25mL of ethyl acetate. Combined extracts were dried over magnesium sulfate and concentrated. Purification by chromatography , eluting with 50% ethyl acetate in hexane gave 40mg of 2-[3-(4-chloro-benzyl)-bicyclo[3.2.1]oct-8-ylidenemethyl]-1H-benzimidazole.

Step 5:

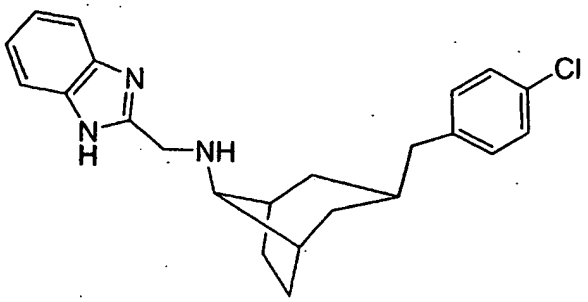


2-[3 –exo-(4-Chloro-benzyl)-bicyclo[3.2.1]oct-8-yl-exo-methyl]-1H-benzimidazole:

Hydrogenation of 40mg of the ethylene ketal of 3-(4-chloro-benzylidene)-bicyclo[3.2.1]octan-8-one over 0.05g of 5% platinum on carbon in 10mL of ethanol under 1atm of hydrogen for 3h gave 40mg of 2-[3-(4-chloro-benzyl)-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole as a mixture of 3-exo-8-exo and 3-exo-8-endo isomers. Preparative TLC eluting with 50% ethyl acetate in hexane gave two bands. The major upper band was the 3-exo-8-exo 2-[3-(4-chloro-benzyl)-

bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: ^{1}H NMR (m+1) = 321.4; ^{1}H NMR (400MHz, $CDCl_3$) 7.6 (m, 2H), 7.2 (m, 7H), 4.85 and 4.8 (2 x d, 1H), 2.6 and 2.42 (2 x d, 2H).

EXAMPLE 5



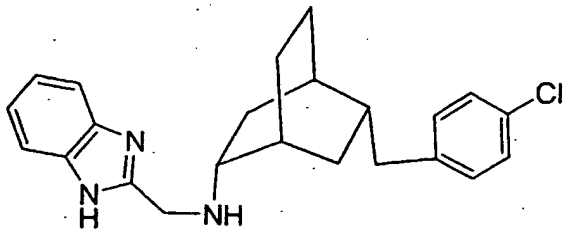
(1H-Benzimidazol-2-ylmethyl)-[3-(4-chloro-benzyl)-bicyclo[3.2.1]oct-8-yl]-amine:

A mixture of 250mg of 3:1 mixture of exo and endo 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one, 400mg of 2-aminomethylbenzimidazole dihydrochloride, 150mg of anhydrous sodium acetate, 10mL of 1,2-dichloroethane and 400mg of sodium triacetoxyborohydride was stirred overnight in a stoppered flask. The mixture was diluted with 50mL of chloroform and washed with 20mL of saturated sodium carbonate. The organic extract was dried over magnesium sulfate and concentrated under reduced pressure. Preparative TLC eluting with 225:25:5 chloroform:methanol:concentrated ammonium hydroxide gave in the fastest band the product as a mixture of two isomers. Crystallization and preparative TLC with 75:25:10 tetrahydrofuran:hexane:triethylamine or chromatography on Chiralpak™ AD eluting with 90:10 0.1% diethylamine in hexane:ethanol gave 150mg of pure 3-exo-8-exo (1H-benzimidazol-2-ylmethyl)-[3-(4-chloro-benzyl)-bicyclo[3.2.1]oct-8-yl]-amine: RT = 5.8 min; MS (m+1) = 380.9; ^{1}H NMR (400MHz, $CDCl_3$) 9.5 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m, 4H), 7.1 (d, 2H), 4.1 (s, 2H), 2.8 (m, 1H), 2.5 (d, 2H), 2.1 (s, 2H), 2- 1.2 (complex, 11H).

Later fractions gave 50mg of pure 3-endo-8-exo (1H-benzimidazol-2-ylmethyl)-[3-(4-chloro-benzyl)-bicyclo[3.2.1]oct-8-yl]-amine: RT = 9min; MS (m+1) = 380.9; ^{1}H NMR (400MHz, $CDCl_3$) 9.5 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m,

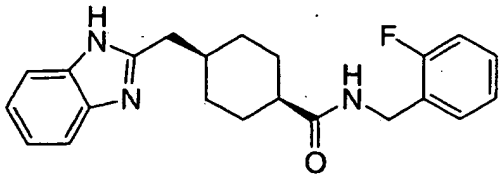
4H), 7.1 (d, 2H), 4.18 (s, 2H), 2.82 (m, 1H), 2.78 (d, 2H), 2.06 (s, 2H), 2.1 - 1.2 (complex, 11H).

EXAMPLE 6



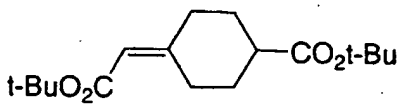
(1H-Benzimidazol-2-ylmethyl)-[5-(4-chloro-benzyl)-bicyclo[2.2.2]oct-2-yl]-amine: Example 6 was prepared in a similar manner to Examples 4 and 5 above. A mixture of 250mg of 3:1 mixture of exo and endo 5-(4-chloro-benzyl)-bicyclo[2.2.2]octan-2-one was prepared from 5-acetoxy-5-cyanobicyclo[2.2.2]octan-2-one in three sequential steps without isolating intermediate products. The first two steps were similar to those described in Steps 1 and 2 of Example 4 above, sequential treatment with sodium borohydride in ethanol, sodium hydroxide, formed 5-hydroxy-bicyclo[2.2.2]octan-2-one. Olefination, hydrogenation, and Swern oxidation of the product, 5-(4-chloro-benzyl)-bicyclo[2.2.2]octan-2-ol followed. To the resulting product was added 400mg of 2-aminomethylbenzimidazole dihydrochloride, 150mg of anhydrous sodium acetate, 10mL of 1,2-dichloroethane and 400mg of sodium triacetoxyborohydride, and stirred overnight in a stoppered flask. The mixture was diluted with 50mL of chloroform and washed with 20mL of saturated sodium carbonate. The organic extract was dried over magnesium sulfate and concentrated under reduced pressure. Preparative TLC eluting with 95:5:5 ethyl acetate:methanol:triethyl amine gave (1H-benzimidazol-2-ylmethyl)-[5-(4-chloro-benzyl)-bicyclo[2.2.2]oct-2-yl]-amine as a racemic mixture of four diastereomers: MS (m+1) = 380.9; ^{1}H NMR (400MHz, $CDCl_3$) 7.6 (br s, 1H), 7.2 (m, 4H), 7.05 (m, 2H), 4.04 and 4.06 (2 x s, 2H), 2.85 (m, 1H), 2.6-5 (m, 3H), 2.0 – 1.0 (complex, 12H).

EXAMPLE 7



Cis-4-(1*H*-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide

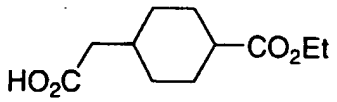
Example 7 was prepared by the following procedure, referring to **Scheme 4** above:



(B)

4-*tert*-Butoxycarbonylmethylene-cyclohexanecarboxylic acid ethyl ester (Compound B):

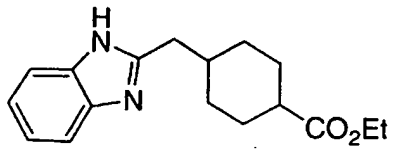
To a solution of ethyl 4-oxocyclohexanecarboxylate **(Compound A)** (8.3g, 48.8mmol), *tert*-butyl diethylphosphonoacetate (13.5g, 53.7mmol), and activated 4Å sieves (30g) in anhydrous THF (250mL) at reflux was added anhydrous LiOH (3.8g, 161.0mmol) in small portions. After refluxing 6h, the reaction was cooled and partitioned between water and ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated to give 13g of a colorless oil. Flash chromatography on silica (10% EtOAc in hexane) yielded **(B)** 4-*tert*-butoxycarbonylmethylene-cyclohexanecarboxylic acid tert-butyl ester (12.5g, 95%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.60 (s, 1 H), 4.15 (q, 2 H), 3.60 (m, 1 H), 2.55 (m, 1 H), 2.35 (m, 1 H), 2.21-2.02 (m, 4 H), 1.78-1.62 (m, 2 H), 1.48 (s, 9 H), 1.25 (t, 3 H); mass spectrum *m/z* 213 [$(M\text{-}tBu)^+$; calcd for $C_{11}H_{17}O_4$: 213].



(C)

4-Carboxymethyl-cyclohexanecarboxylic acid ethyl ester (C):

A solution of diester **(B)** (12.5g, 46.3mmol) and 10% palladium on activated carbon (5g) in absolute ethanol (200mL) was exposed to a hydrogen atmosphere (at balloon pressure) and stirred vigorously for 1h. After removal of catalyst by filtration and concentration, the resultant colorless oil was dissolved in methylene chloride (150mL) and TFA (75mL) and stirred for 15min. All volatiles were removed by rotary evaporation and the resultant colorless oil placed under high vacuum to give (C) 4-carboxymethyl-cyclohexanecarboxylic acid ethyl ester (9.9g, 99%) as a white solid. Data for cis/trans mixture: ^{1}H NMR (400MHz, CD_3OD) δ 4.13 (2q, 4 H), 2.58 (m, 1H), 2.30-2.20 (m, 1 H), 2.20 (2d, 4 H), 2.05-1.80 (m, 7 H), 1.80-1.55 (m, 5 H), 1.50-1.38 (m, 3 H), 1.32-1.25 (m, 1 H), 1.25 (2t, 6 H), 1.10-1.00 (m, 2 H) ; mass spectrum *m/z* 215 [$(M+H)^+$; calcd for $C_{11}H_{19}O_4$: 215].

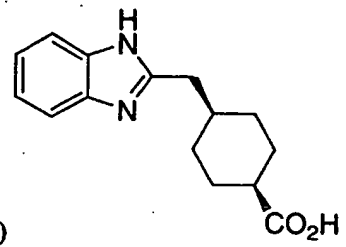


(D)

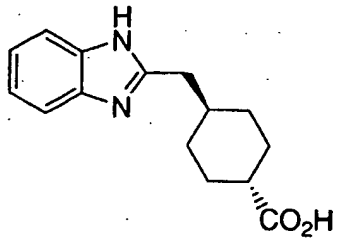
4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid ethyl ester (D):

To a solution of acid (C) (10.5g, 49.0mmol), EDC (9.4g, 49.0mmol) and HOAt (6.7g, 49.0mmol) in 80mL anhydrous DMF was added phenylenediamine (5.3g, 49.0mmol) and the reaction mixture stirred for 1h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc and the organic portion washed 3x with water. The organic layer was dried with $MgSO_4$ and concentrated to yield 14g of a yellow oil. The crude material was dissolved in toluene/TFA (1:1 300mL), heated to 90°C and stirred overnight. The reaction mixture was then concentrated and purified by column chromatography on silica using 1:1 EtOAc/hexane followed by 90:10:1 CH_2Cl_2/MeOH/NH_4OH to give **(D)** 4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid ethyl ester (7.5g, 53%) as a

colorless oil. Data for cis/trans mixture: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.62 (2d, 4 H), 7.38 (2d, 4 H), 2.70 (2d, 4 H), 2.48 (m, 1 H), 2.10-1.90 (m, 5 H), 1.70-1.58 (m, 4 H), 1.60-1.53 (m, 3 H), 1.49-1.38 (m, 4 H), 1.63-1.50 (m, 1 H), 1.40 (2t, 6 H), 0.90-0.70 (m, 2 H); mass spectrum *m/z* 287 [$(M+H)^+$; calcd for $C_{17}H_{23}N_2O_2$: 287].



(E)



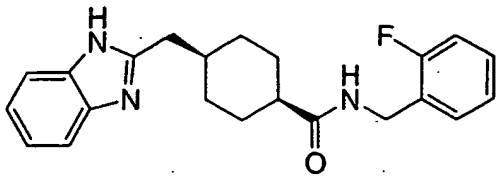
(F)

Cis-4-(1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid (E):

The cis/trans mixture of 4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid ethyl esters **(D)** (600mg, 2.1mmol) was dissolved in a minimal amount of THF (5mL) and mixed with concentrated aqueous LiOH (2mL). The reaction was stirred vigorously and heated at 65°C for 3h. After cooling and concentration, the crude material was dissolved in 1:1 water/CH_3CN and subjected to preparative reverse-phase HPLC to yield **(E)** cis-4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid (200mg, 37%): ^{1}H NMR (400MHz, CD_3OD) δ 7.77 (m, 2 H), 7.60 (m, 2 H), 3.11 (d, 2 H), 2.62 (m, 1 H), 2.10 (m, 3 H), 1.65 (m, 4 H), 1.43 (m, 2 H); mass spectrum *m/z* 259 [$(M+H)^+$; calcd for $C_{15}H_{19}N_2O_2$: 259].

Later fractions gave the trans isomer **(F)** (276mg, 51%): ^{1}H NMR (400MHz, CD_3OD) δ 7.77 (m, 2 H), 7.59 (m, 2 H), 3.08 (d, 2 H), 2.28 (m, 1 H), 2.05 (d, 2 H), 1.95 (m, 1 H), 1.84 (d, 2 H), 1.46 (dq, 2 H), 1.20 (dq, 2 H); mass spectrum *m/z* 259 [$(M+H)^+$; calcd for $C_{15}H_{19}N_2O_2$: 259].

Example 7:

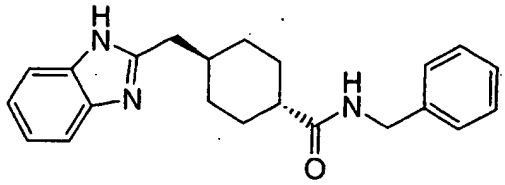


(Ex. 7)

Cis-4-(1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide:

To a solution of **(E)** cis-4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid (271mg, 1.05mmol), EDC (200mg, 1.05mmol) and HOAt (142mg, 1.05mmol) in anhydrous DMF (4mL) was added 2-fluorobenzylamine (131mg, 1.05mmol) and the reaction mixture was stirred for 1h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc and the organic layer washed 2x with water. The EtOAc was dried with $MgSO_4$ and concentrated to give a yellow solid. The crude material was triturated with 2:2:1 water/CH_3CN/DMSO and the resultant white solid filtered off. Repetitive concentration and trituration of the filtrate in the same manner gave cis-4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide **(F)** (230mg, 60%) as a white solid. The **(F)** compound was stirred in 1M HCl/ether (10mL) for 1h and concentrated to give the HCl salt of **Ex. 7** (250mg): ^{1}H NMR (400MHz, CD_3OD) δ 7.50 (br s 2 H), 7.35-7.25 (m, 2 H), 7.22-7.05 (m, 4 H), 4.43 (s, 2 H), 2.92 (d, 2 H), 2.41 (m, 1 H), 2.23 (m, 1 H), 1.93 (m, 2 H), 1.60 (m, 6 H); mass spectrum *m/z* 366 [$(M+H)^+$; calcd for $C_{22}H_{25}N_3OF$: 366].

EXAMPLE 8



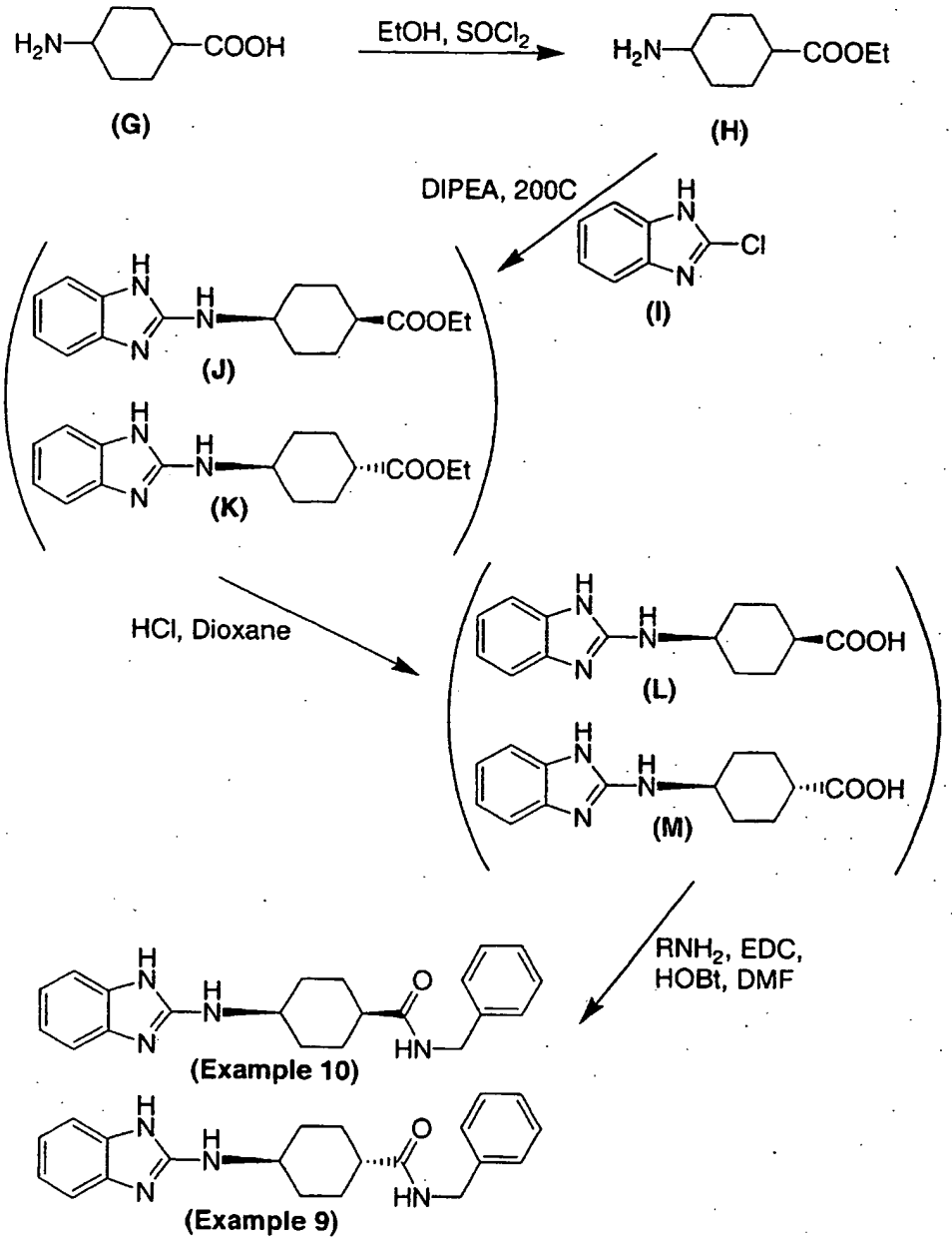
Trans-4-(1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide

Example 8 was prepared by the following procedure. To a solution of trans-4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid (**F**) (444mg, 1.72mmol), EDC (328mg, 1.72mmol) and HOAt (234mg, 1.72mmol) in anhydrous DMF (4mL) was added benzylamine (184mg, 1.72mmol). The resulting reaction mixture was stirred for 15h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc and the organic layer washed 2x with water, and dried with $MgSO_4$. Concentration gave trans-4-(1H-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide (400mg, 67%) as a white solid. ^{1}H NMR (400MHz, CD_3OD) δ 7.49 (br s, 2 H), 7.30-7.17 (m, 7 H), 4.34 (s, 2 H), 2.78 (d, 2 H), 2.21 (m, 1 H), 1.84 (m, 5 H), 1.55 (q, 2 H), 1.16 (q, 2 H); mass spectrum *m/z* 348 [$(M+H)^+$; calcd for $C_{22}H_{26}N_3O$: 348].

All compounds analogous to **Example 8** were prepared from carboxylic acid (**F**) via the above procedure using the appropriate amine and purified by reverse-phase HPLC.

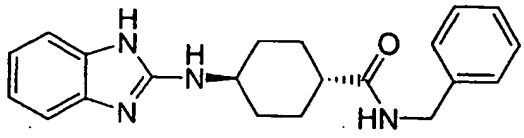
Compounds of the present invention can be prepared according to **Scheme 7** shown below:

Scheme 7


H2N
COOH
(G)
EtOH, SOCl2
H2N
COOEt
(H)
DIPEA, 200C
Cl
(I)
COOEt
(J)
COOEt
(K)
HCl, Dioxane
COOH
(L)
COOH
(M)
RNH2, EDC,
HOBt, DMF
O
HN
(Example 10)
O
HN
(Example 9)

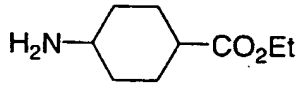
5

EXAMPLE 9



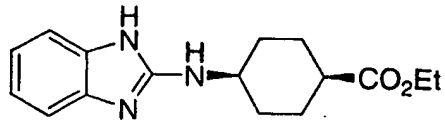
Trans-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide

Referring to **Scheme 7** above, **Example 9** was prepared by the following procedure.

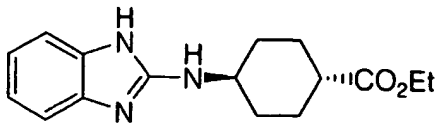


4-Amino-cyclohexanecarboxylic acid ethyl ester (H):

To a suspension of 4-amino-cyclohexanecarboxylic acid (**G**) (5g, 35mmol) in EtOH (175mL) at 0°C was added $SOCl_2$ (12.6mL, 174mmol) dropwise via a syringe. The reaction mixture was warmed to room temperature and stirred for 16h. After concentration of the reaction mixture, ether was added and the suspension was filtered to give 4-amino-cyclohexanecarboxylic acid ethyl ester (**H**) (mixture of cis/trans) as a white solid (4.8g): ^{1}H NMR (300MHz, $CDCl_3$) δ 8.35 (br s, 3 H), 4.18 (m, 2 H), 3.36-3.15 (m, 1 H), 2.54 (m, 1 H), 2.30-1.45 (series of m, 8 H), 1.13 (t, 3 H); mass spectrum *m/z* 172 [$(M+H)^+$; calcd for $C_9H_{18}NO_2$: 172].



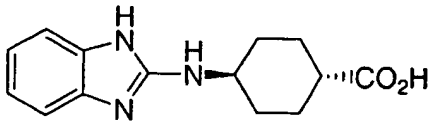
(J)



(K)

Cis-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (J) and Trans-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (K):

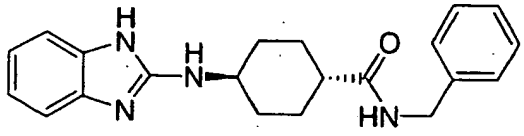
A mixture of 2-Chlorobenzimidazole (**I**) (0.9g, 5.9mmol) and ethyl-4-amino-cyclohexane carboxylate (1.1g, 5.4mmol) were placed in a glass high pressure tube. Diisopropylethylamine (2.8mL, 16.2mmol) was added, the reaction vessel was sealed and heated to 200°C for 4h and allowed to cool to room temperature. Next was added 5mL EtOH and heated to dissolve the reaction mixture. The reaction mixture was partitioned between aqueous $NaHCO_3$ and EtOAc, and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. Purification of the crude product on silica gel (gradient, 1:1 hexanes:EtOAc to EtOAc) gave the cis 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (**J**) (0.5g) and the trans 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (**K**) (0.5g). Data for (**J**): ^{1}H NMR (300MHz, $CDCl_3$) δ 7.28 (br s, 2 H), 7.02 (m, 2 H), 5.16 (br s, 1 H), 4.15 (q, 2 H), 3.97 (br s, 1 H), 2.40 (br s, 1 H), 1.80-1.54 (m, 8 H), 1.22 (t, 3 H); mass spectrum *m/z* 288 $[(M+H)^+$; calcd for $C_{16}H_{22}N_3O_2$: 288]. Later fractions gave the trans isomer (**K**) (0.5g): ^{1}H NMR (300MHz, $CDCl_3$) δ 7.28 (br s, 2 H), 7.02 (m, 2 H), 4.82 (br s, 1 H), 4.15 (q, 2 H), 3.64 (m, 1 H), 2.20 (br d, 3 H), 1.96 (br d, 2 H), 1.42 (m, 2 H), 1.22 (t, 3 H), 1.20 (m, 2 H); mass spectrum *m/z* 288 $[(M+H)^+$; calcd for $C_{16}H_{22}N_3O_2$: 288].



Trans-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid (M):

A solution of trans 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (**K**) (500mg, 1.7mmol) in dioxane (4mL) and

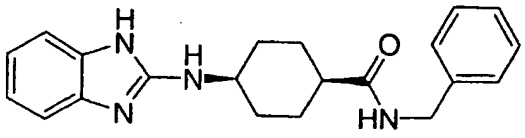
HCl (6 N, 8mL) was heated to 60°C for 16h. After cooling, concentration of the reaction mixture gave trans 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid as a white solid (M) (420mg): ^{1}H NMR (300MHz, CD_3OD) δ 7.39 (m, 2 H), 7.28 (m, 2 H), 3.57 (m, 1 H), 2.35 (m, 1 H), 2.18 (br t, 4 H), 1.65-1.40 (m, 4 H); mass spectrum *m/z* 260 [$(M+H)^+$; calcd for $C_{14}H_{18}N_3O_2$: 260].



Example 9, Trans-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide:

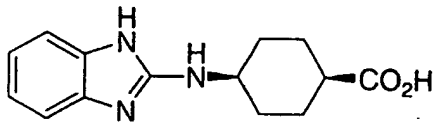
To a solution of trans 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid (M) (20mg, 0.07mmol) in DMF (0.2mL) was added EDC (26mg, 0.14mmol), HOBt (18mg, 0.14mmol), triethylamine (0.019mL, 0.14mmol) and benzyl amine (0.007mL, 0.7mmol). The reaction mixture was stirred at room temperature for 1h followed by quenching with aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic was washed twice with water, dried over Na_2SO_4, filtered and concentrated. Purification of the crude oil by preparative reverse-phase HPLC gave trans 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide (**Example 9**) (14mg): ^{1}H NMR (300MHz, CD_3OD) δ 7.40-7.20 (m, 9 H), 4.39 (s, 2 H), 3.55 (m, 1 H), 2.31 (m, 1 H), 2.20 (br d, 2 H), 1.98 (br d, 2 H), 1.77 (m, 2 H), 1.50 (m, 2 H); mass spectrum *m/z* 349 [$(M+H)^+$; calcd for $C_{21}H_{25}N_4O$: 349].

EXAMPLE 10



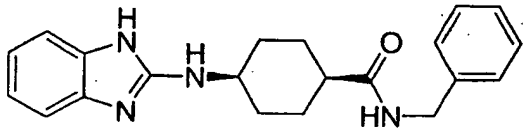
Example 10, Cis-4-(1*H*-benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide:

Referring to Scheme 7, Example 10 was prepared by the following procedure.



Cis-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid (L):

In a similar manner to **Example 9** above, cis 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (J) was saponified and gave the cis 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid (L): ^{1}H NMR (300MHz, CD_3OD) δ 7.39 (m, 2 H), 7.28 (m, 2 H), 3.64 (m, 1 H), 2.60 (m, 1 H), 2.10 m, 2 H), 1.95 (m, 2 H), 1.81-1.65 (m, 4 H); mass spectrum *m/z* 260 [$(M+H)^+$; calcd for $C_{14}H_{18}N_3O_2$: 260].

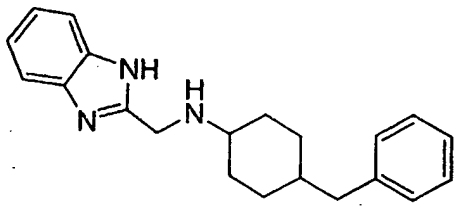


Example 10, Cis-4-(1*H*-benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide:

To a solution of cis 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid (L) (20mg, 0.07mmol) in DMF (0.2mL) was added EDC (26mg, 0.14mmol), HOBt (18mg, 0.14mmol), triethylamine (0.019mL, 0.14mmol) and benzyl amine (0.007mL, 0.7mmol). The reaction mixture was stirred at room temperature for 1h followed by quenching with aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic was washed twice with water, dried over Na_2SO_4, filtered and concentrated. Purification of the crude oil by preparative reverse-phase HPLC gave cis 4-(1H-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide **(Example 10)** (12mg): ^{1}H NMR (300MHz, CD_3OD) δ 7.40-7.20 (m, 9 H), 4.39 (s, 2 H), 3.81 (m, 1 H), 2.45 (m, 1 H), 2.02-1.77 (m, 8 H); mass spectrum *m/z* 349 [$(M+H)^+$; calcd for $C_{21}H_{25}N_4O$: 349].

All compounds analogous to **Example 10** were prepared from carboxylic acid (M) via the above procedure using the appropriate amine and purified by reverse-phase HPLC.

EXAMPLE 11

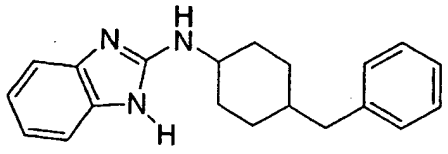


(1H-Benzimidazol-2-ylmethyl)-(4-benzyl-cyclohexyl)-amine

Example 11 was prepared in a manner similar to Example 5, but substituting 4-benzyl-cyclohexanone, the product of Example 1, Step 3, for exo and endo 3-(4-chloro-benzyl)-bicyclo[3.2.1]octan-8-one. The procedure gave a 1:1 mixture of cis and trans (1H-benzoimidazol-2-ylmethyl)-(4-benzyl-cyclohexyl)-amine. Chromatography on Chiralpak™ OD eluting with 60:40 of 0.1% diethylamine in hexane:2-propanol gave first (1H-benzoimidazol-2-ylmethyl)-(4-*cis*-benzyl-cyclohexyl)-amine: RT = 4.69min; MS (m+1) = 320; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.6 (m, 2H), 7.35 -7.25 (m, 5H), 7.18 (m, 2H), 4.2 (s, 2H), 2.85 (m, 1H), 2.55 (d, 2H), 1.75 (m, 3H), 1.7-1.55 (m, 2H), 1.5 (m, 2H), 1.4 (m, 3H).

Later fractions gave (1H-benzoimidazol-2-ylmethyl)-(4-*trans*-benzyl-cyclohexyl)-amine: RT = 5.67min; MS (m+1) = 320; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.6 (m, 2H), 7.35 -7.25 (m, 5H), 7.18 (m, 2H), 4.2 (s, 2H), 2.5 (d, 2H), 1.95 (d, 2H), 1.72 (d, 2H), 1.7-1.55 (m, 2H), 1.5 (m, 2H), 1.4 (m, 3H).

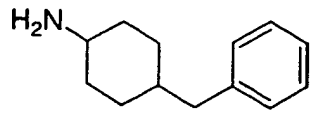
EXAMPLE 12



(1H-Benzimidazol-2-yl)-(4-benzyl-cyclohexyl)-amine

Example 12 was prepared by the following procedure.

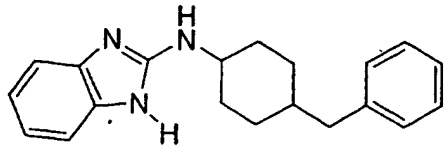
Step 1:



4-Benzyl-cyclohexylamine:

A mixture of 2g of 4-benzylcyclohexanone, the product of Example 1, Step 3, 16g of ammonium acetate, 100mL of methanol and 2.5g of sodium cyanoborohydride was stirred for 5 days at room temperature. After cooling in an ice bath, the reaction was carefully quenched in an efficient fume hood by dropwise addition of 25mL of 1N HCl. After stirring for 10min, sodium hydroxide pellets were added to the cold solution until the pH (indicator paper) was about 10. The mixture was concentrated under reduced pressure, diluted with 100mL of water, made basic by addition of more sodium hydroxide pellets and extracted into 4X100mL portions of chloroform. After drying over magnesium sulfate, the extracts were concentrated under reduced pressure and then dried under vacuum overnight. Analysis by TLC (silica gel, elution with 90:10:1 chloroform:methanol:conc. ammonium hydroxide) indicated no 4-benzylcyclohexanone or 4-benzylcyclohexanol was present, only 2 new bands which correspond to a mixture of cis- and trans 4-benzyl-cyclohexylamine, which was an oil.

Step 2:



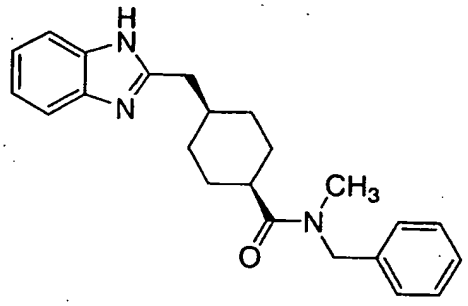
(1H-Benzimidazol-2-yl)-(4-benzyl-cyclohexyl)-amine:

Following the sample experimental procedure described by J.J. Perkins, A.E. Zartman, and R.S. Meissner, *Tetrahedron Letters*, 40:1103-1106(1999), but substituting a mixture of cis- and trans 4-benzyl-cyclohexylamine for cyclohexylamine, gave a mixture of cis and trans (1H-benziimidazol-2-yl)-(4-benzyl-

cyclohexyl)-amine. Chromatography on silica gel eluting with 90:10 chloroform:methanol gave (1H-benziimidazol-2-yl)-(4-*cis* -benzyl-cyclohexyl)-amine: MS (m+1) = 306; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.42 (d, 2H), 2.10 (d, 2H), 1.70 (d, 2H).

Later fractions gave (1H-benziimidazol-2-yl)-(4-*trans* -benzyl-cyclohexyl)-amine: MS (m+1) = 306; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.55 (m, 2H), 2.15 (d, 2H), 1.70 (d, 2H).

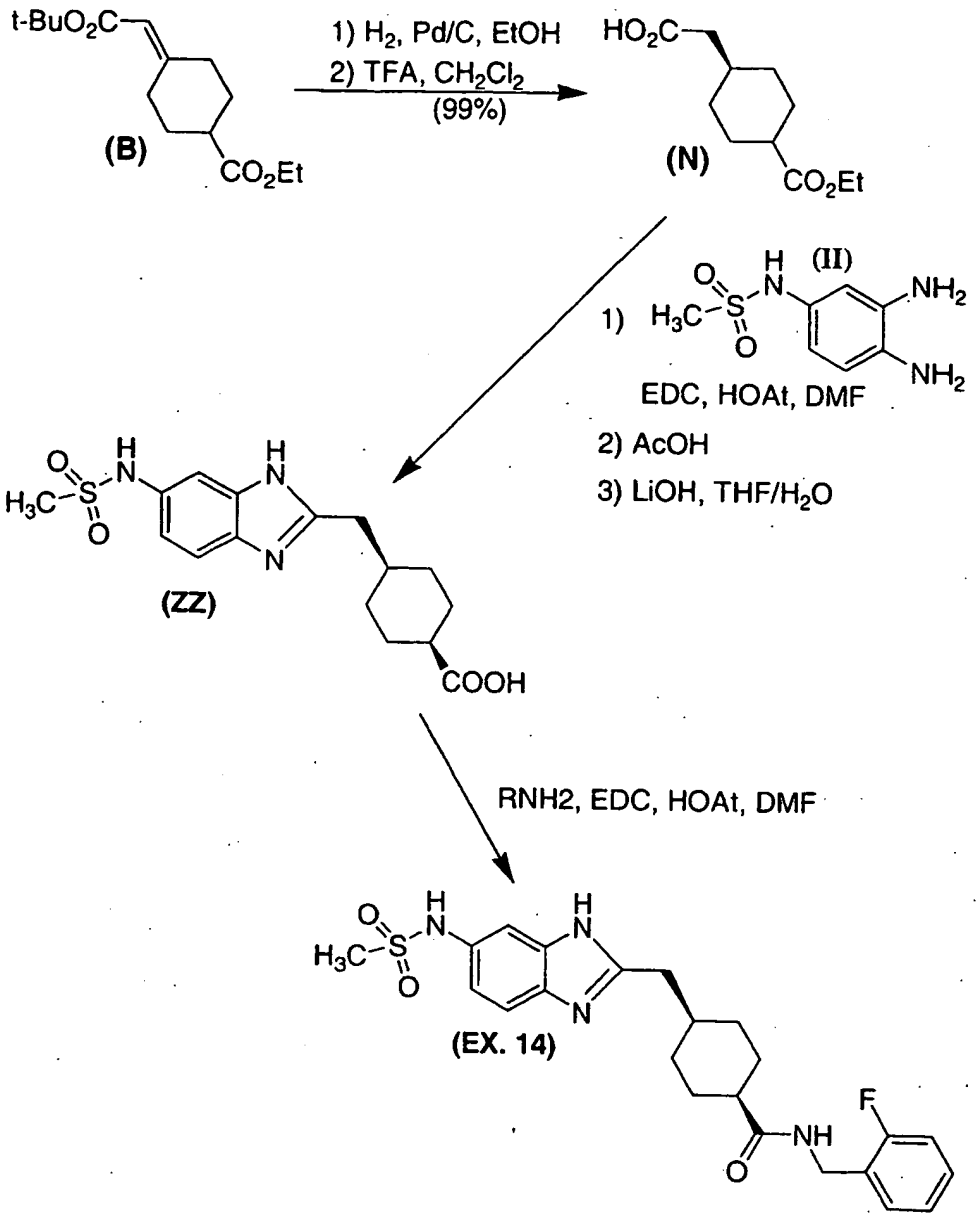
EXAMPLE 13



Ex. 13

Example 13 was prepared by following the above procedure for **Example 7** except using N-methylbenzylamine instead of 2-fluorobenzylamine: mass spectrum *m/z* 361 [$(M+H)^+$; calcd for $C_{23}H_{28}N_3O$: 362].

Compounds of the present invention can be prepared according to **Scheme 8** shown below:

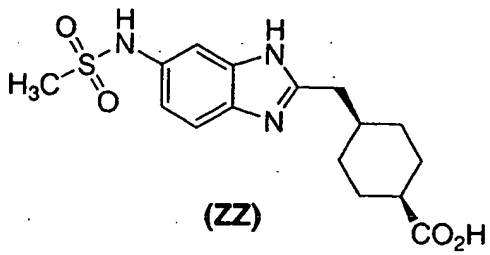


Compound (N)

Olefin (B) (0.3g, 1.18mmol) was dissolved in EtOAc (5mL) and cooled to –20°C. Rh on alumina catalyst (0.06g) was added, the reaction vessel was pressurized to 1500psi with hydrogen gas, and the mixture was shaken for 5h. After removal of the catalyst by filtration and concentration, the resultant colorless oil was

dissolved in methylene chloride (5mL) and TFA (3mL) and stirred for 15min. All volatiles were removed by rotary evaporation and the resultant colorless oil placed under high vacuum to give **Compound (N)** as a 6:1 cis to trans mixture.

Compound (ZZ)

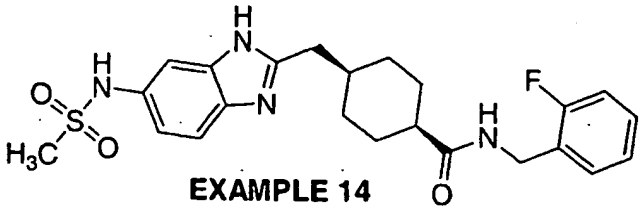


(ZZ)

To a solution of acid **(N)** (300mg, 1.4mmol) in DMF (10mL) was added EDC (268mg, 1.40mmol), HOAt (190mg, 1.40mmol) and methanesulfonic acid (3,4-diamino-phenyl)-amide **(II)** (281mg, 1.40mmol). The reaction mixture was stirred at room temperature for 16h followed by quenching with aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic was washed twice with water, dried over Na_2SO_4, filtered and concentrated.

The resulting crude product was dissolved in acetic acid (10mL) and heated to 130°C for 15min. The reaction mixture was cooled, concentrated and partitioned between aqueous $NaHCO_3$ and EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude oil was used without purification. The crude ester was dissolved in HBr/H_2O (48%, 10mL) and was then heated to 100°C for 30min. The resulting reaction mixture was cooled, concentrated and purified by preparative reverse-phase HPLC, to give **Compound (ZZ)** as the pure cis isomer: ^1H NMR (300MHz, CD_3OD) δ 7.75 (d, 1 H), 7.69 (d, 1 H), 7.39 (dd, 1 H), 3.09 (d, 2 H), 2.99 (s, 3 H), 2.60 (m, 1 H), 2.08 (m, 3 H), 1.62 (m, 4 H);1.40 (m, 2 H) ppm; mass spectrum *m/z* 352 $[(M+H)^+$; calcd for $C_{16}H_{22}N_3O_4S$: 352].

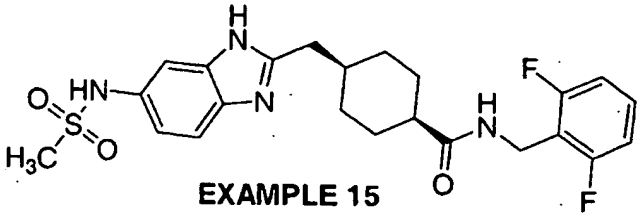
EXAMPLE 14



EXAMPLE 14

Example 14 was prepared by the following procedure: To a solution of **(ZZ)** (10mg, 0.03mmol), EDC (10mg, 0.06mmol) and HOAt (8mg, 0.06mmol) in anhydrous DMF (0.3mL) was added 2-fluorobenzylamine (2mg, 0.06mmol) and the reaction mixture was stirred for 2h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was washed 2x with water. The EtOAc was dried with $MgSO_4$ and concentrated. The resulting crude material was purified by reverse phase HPLC to give **Example 14**: mass spectrum *m/z* 459 $[(M+H)^+$; calcd for $C_{23}H_{28}FN_4O_3S$: 459].

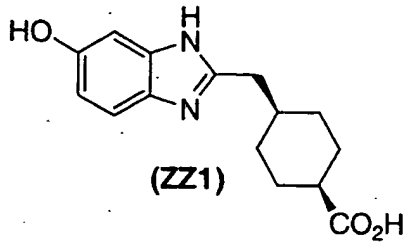
EXAMPLE 15



EXAMPLE 15

Example 15 was prepared by following the above procedure for **Example 14** except 2,6-diflouorobenzylamine was used instead of 2-fluorobenzylamine: mass spectrum *m/z* 477 $[(M+H)^+$; calcd for $C_{23}H_{27}F_2N_4O_3S$: 477].

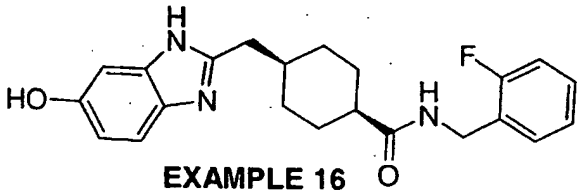
COMPOUND (ZZ1)



(ZZ1)

Compound (ZZ1) was prepared by following the above procedure for **Compound (ZZ)** except 4-methoxy-1,2-phenylenediamine was used instead of methanesulfonic acid (3,4-diamino-phenyl)-amide: mass spectrum *m/z* 275 [$(M+H)^+$; calcd for $C_{15}H_{19}N_2O_3$: 275].

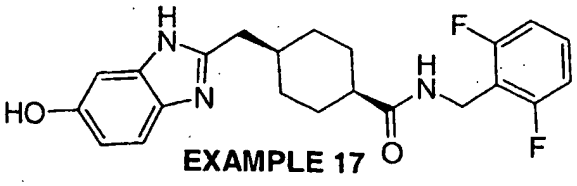
EXAMPLE 16



EXAMPLE 16

Example 16 was prepared by following the above procedure for **Example 14** except **Compound (ZZ1)** was used instead of **Compound (ZZ)**: mass spectrum *m/z* 382 [$(M+H)^+$; calcd for $C_{22}H_{24}FN_3O_2$: 382].

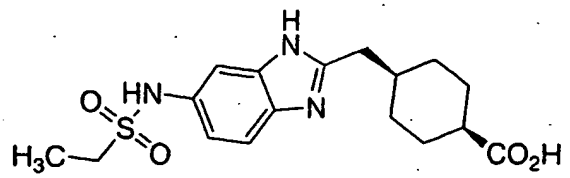
EXAMPLE 17



EXAMPLE 17

Example 17 was prepared by following the above procedure for **Example 15** except **Compound (ZZ1)** was used instead of **Compound (ZZ)**: mass spectrum *m/z* 400 [$(M+H)^+$; calcd for $C_{22}H_{24}F_2N_3O_2$: 400].

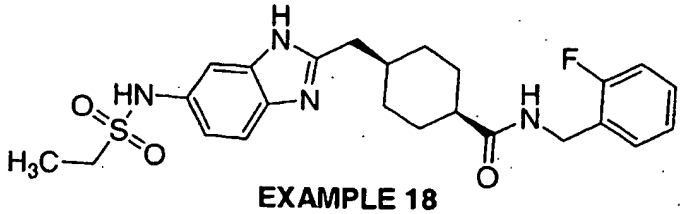
Compound (ZZ2)



(ZZ2)

Compound (ZZ2 was prepared by following the above procedure for **Compound (ZZ)** except ethanesulfonic acid (3,4-diamino-phenyl)-amide was used instead of methanesulfonic acid (3,4-diamino-phenyl)-amide: mass spectrum *m/z* 366 [$(M+H)^+$; calcd for $C_{17}H_{24}N_3O_4S$: 366].

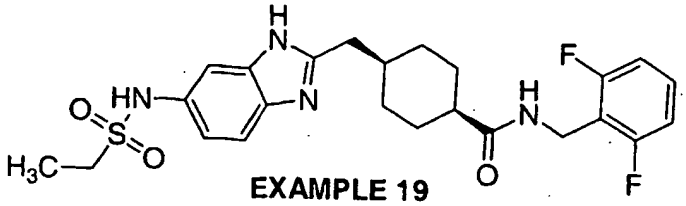
EXAMPLE 18



EXAMPLE 18

Example 18 was prepared by following the above procedure for **Example 14** except **Compound (ZZ2)** was used instead of **Compound (ZZ)**: mass spectrum *m/z* 473 [$(M+H)^+$; calcd for $C_{24}H_{30}FN_4O_3S$: 473].

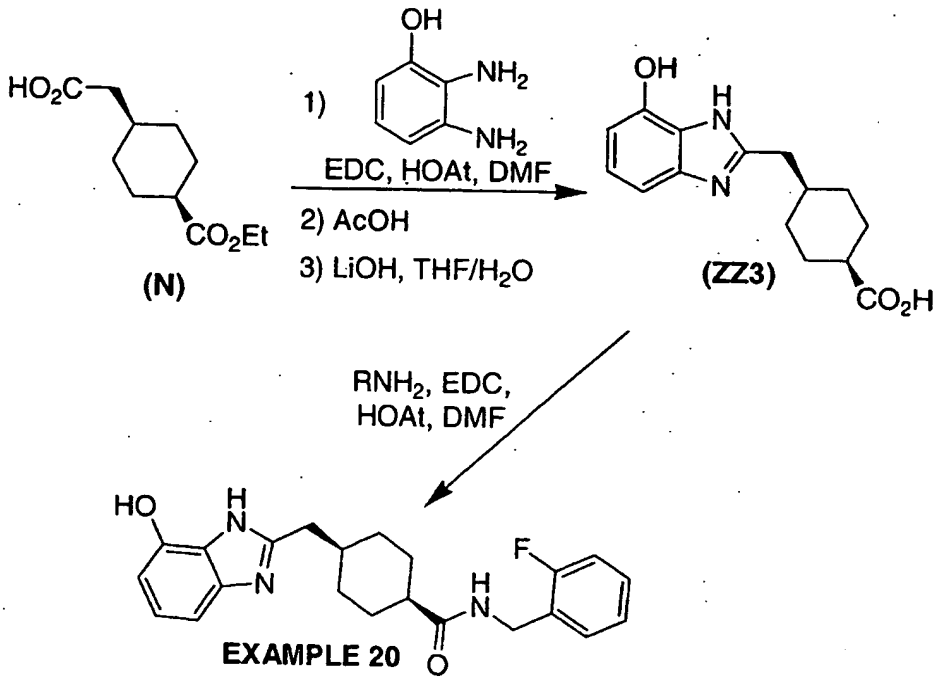
EXAMPLE 19



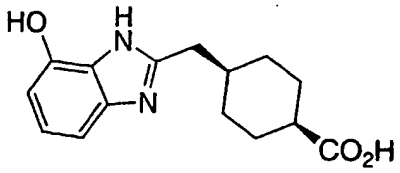
EXAMPLE 19

Example 19 was prepared by following the above procedure for **Example 15** except **Compound (ZZ2)** was used instead of **Compound (ZZ)**: mass spectrum *m/z* 491 [$(M+H)^+$; calcd for $C_{24}H_{29}F_2N_4O_3S$: 491].

Compounds of the present invention can be prepared according to **Scheme 9** shown below:



Preparation of acid **Compound (ZZ3)**:

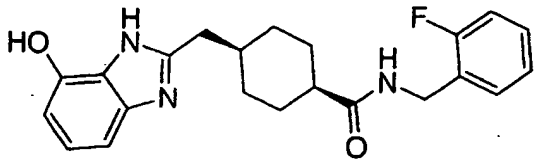


(ZZ3)

Compound (ZZ3) was prepared by following the above procedure for **Compound ZZ** except 3-hydroxy-1,2-phenylenediamine was used instead of

methanesulfonic acid (3,4-diamino-phenyl)-amide: mass spectrum *m/z* 275 [$(M+H)^+$; calcd for $C_{15}H_{19}N_2O_3$: 275].

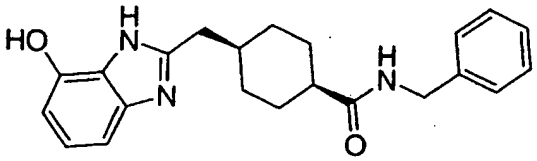
EXAMPLE 20 :



Example 20

Example 20 was prepared by following the above procedure for **Example 14** except **Compound (ZZ3)** was used instead of **Compound (ZZ)**: mass spectrum *m/z* 382 [$(M+H)^+$; calcd for $C_{22}H_{25}FN_3O_2$: xx].

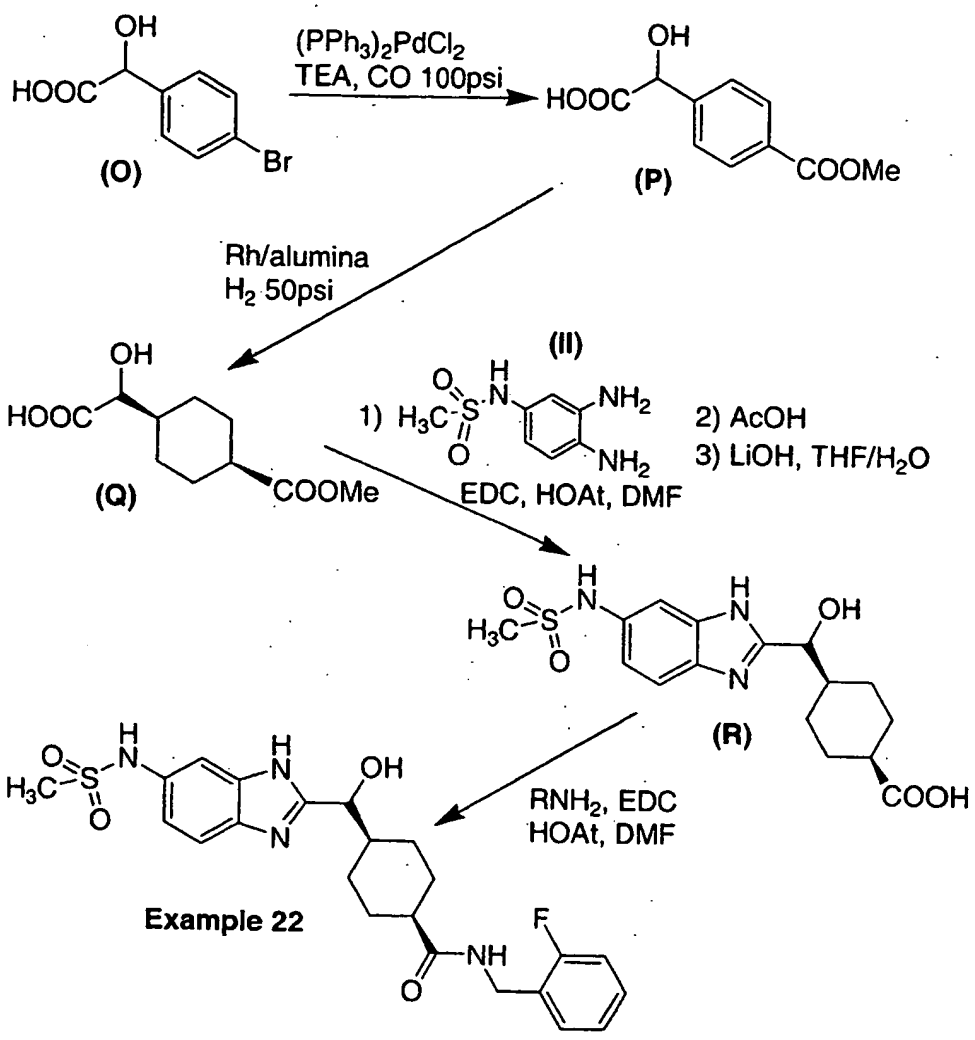
EXAMPLE 21



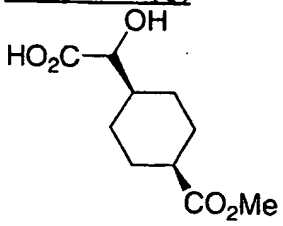
Example 21

Example 20 was prepared by following the above procedure for **Example 14** except **Compound (ZZ3)** was used instead of **Compound (ZZ)**, and benzylamine was used instead of 2-fluorobenzylamine: mass spectrum *m/z* 364 [$(M+H)^+$; calcd for $C_{22}H_{26}N_3O_2$: 364].

Compounds of the present invention can be prepared according to **Scheme 10** shown below:



Compound (Q):



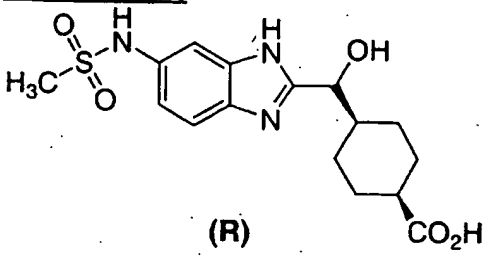
(Q)

4-Bromomandelic acid (O) (3.0g, 13.0mmol) was dissolved in MeOH (75mL) and placed in a pressure bomb. To that resulting solution was added

$(PPh_3)_2PdCl_2$ (0.91g, 1.3mmol) and triethylamine (5.4mL, 39mmol). The reaction mixture was pressurized with CO (100psi) and heated to 100°C for 60h. After cooling, the mixture was filtered, concentrated and purified by reverse phase HPLC to give ester (**P**): ^{1}H NMR (400MHz, CD_3OD) δ 8.03 (d, 2 H), 7.61 (d, 2 H), 5.25 (s, 1 H), 3.90 (s, 3 H) ppm.

Compound (**P**) (0.35g, 1.7mmol) was dissolved in MeOH (10mL) and Rh on alumina catalyst (0.05g) was added. The reaction vessel was pressurized to 50psi with hydrogen gas, and the mixture was shaken for 24h. After filtration and concentration, the product (**Q**) was used without purification as a 3:1 cis:trans mixture of isomers: mass spectrum *m/z* 217 [$(M+H)^+$; calcd for $C_{10}H_{17}O_5$: 217].

Compound (R):

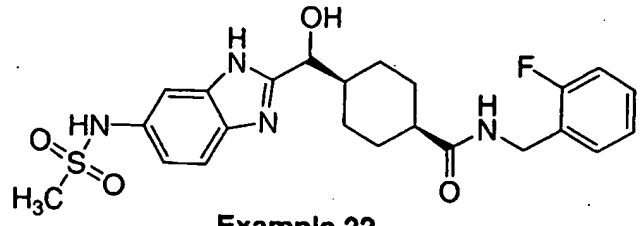


To a solution of acid (**Q**) (100mg, 0.46mmol) in DMF (6mL) was added EDC (97mg, 0.51mmol), HOAt (70mg, 0.51mmol) and methanesulfonic acid (3,4-diamino-phenyl)-amide (**II**) (100mg, 0.46mmol). The reaction mixture was stirred at room temperature for 1h followed by quenching with aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic was washed twice with water, dried over Na_2SO_4, filtered and concentrated.

The resulting crude product was dissolved in acetic acid (5mL) and heated to 130°C for 15min. The reaction mixture was cooled, concentrated and partitioned between aqueous $NaHCO_3$ and EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was without purification.

The crude ester was dissolved in HBr/H_2O (48%, 3mL) and then was heated to 100°C for 10min. The reaction mixture was cooled, concentrated and purified by preparative reverse-phase HPLC, to give (**R**) as the pure cis isomer: mass spectrum *m/z* 368 [$(M+H)^+$; calcd for $C_{16}H_{22}N_3O_5S$: 368].

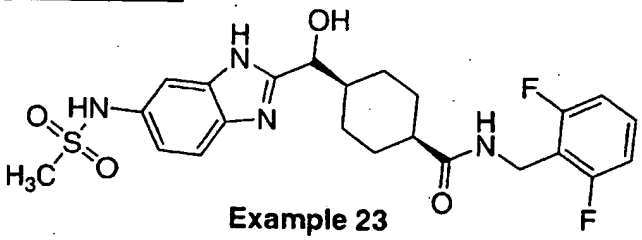
EXAMPLE 22



Example 22

Example 22 was prepared by the following procedure: To a solution of **(R)** (35mg, 0.1mmol), EDC (36mg, 0.2mmol) and HOAt (26mg, 0.2mmol) in anhydrous DMF (2mL) was added 2-fluorobenzylamine (24mg, 0.2mmol) and the resulting reaction mixture was stirred for 3h. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the organic layer washed 2x with water. The EtOAc was dried with $MgSO_4$ and concentrated. The resulting crude material was purified by reverse phase HPLC to give **Example 22**: ^1H NMR (300MHz, CD_3OD) δ 7.74 (m, 2 H), 7.41 (d, 1 H), 7.25 (m, 2 H); 7.09 (m, 2 H), 5.06 (d, 1 H), 4.40 (s, 2 H), 3.00 (s, 3 H), 2.47 (m, 1 H), 2.10 (m, 3 H), 1.6 (m, 6 H) ppm; mass spectrum *m/z* 475 $[(M+H)^+$; calcd for $C_{23}H_{28}FN_4O_4S$: 475].

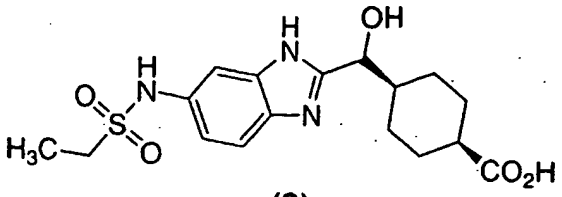
EXAMPLE 23



Example 23

Example 23 was prepared by following the above procedure for **Example 22** except 2,6-diflouorobenzylamine was used instead of 2-fluorobenzylamine: mass spectrum *m/z* 493 $[(M+H)^+$; calcd for $C_{23}H_{27}F_2N_4O_4S$: 493].

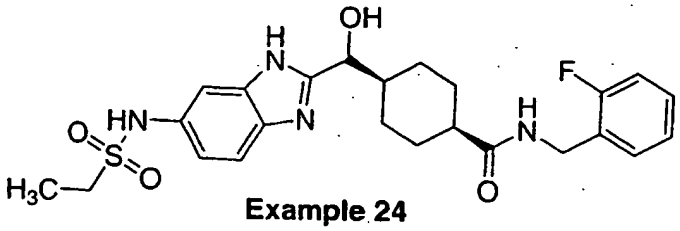
Compound (S):



(S)

Compound (S) was prepared by following the above procedure for **(R)** except ethanesulfonic acid (3,4-diamino-phenyl)-amide was used instead of methanesulfonic acid (3,4-diamino-phenyl)-amide: mass spectrum *m/z* 382 $[(M+H)^+$; calcd for $C_{17}H_{24}N_3O_5S$: 382].

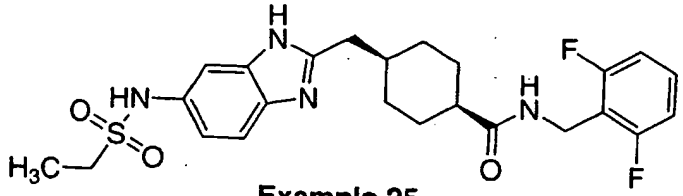
EXAMPLE 24



Example 24

Example 24 was prepared by following the above procedure for **Example 22** except acid **(S)** was used instead of **(R)**: mass spectrum *m/z* 489 $[(M+H)^+$; calcd for $C_{24}H_{30}FN_4O_4S$: 489].

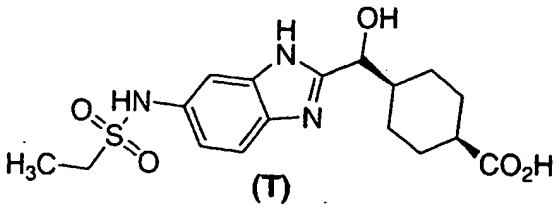
EXAMPLE 25



Example 25

Example 25 was prepared by following the above procedure for **Example 23** except acid **Compound (S)** was used instead of **Compound (R)**: mass spectrum *m/z* 507 $[(M+H)^+$; calcd for $C_{24}H_{29}F_2N_4O_4S$: 507].

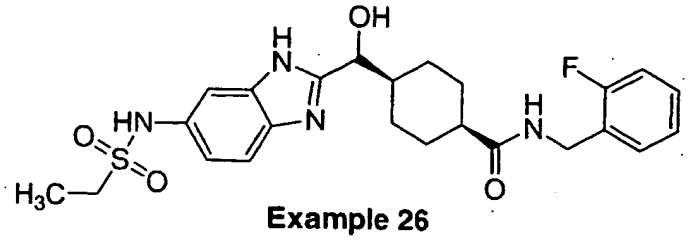
Compound (T):



(T)

Acid (T) was prepared by following the above procedure for **Compound (R)** except phenylene diamine was used instead of methanesulfonic acid (3,4-diamino-phenyl)-amide: mass spectrum *m/z* 275 [$(M+H)^+$; calcd for $C_{15}H_{19}N_2O_3$: 275].

EXAMPLE 26



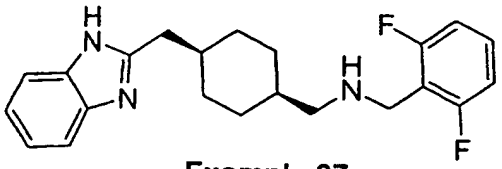
Example 26

Example 26 was prepared by following the above procedure for **Example 22** except acid **(T)** was used instead of **Compound (R)**: mass spectrum *m/z* 382 [$(M+H)^+$; calcd for $C_{22}H_{25}FN_3O_2$: 382].

EXAMPLES 26a and 26b :

Racemate **Example 26** was separated into its enantiomers by chiral HPLC on a Chiralpack AD column (250x4.6cm) eluting with 75% hexane +0.1% diethylamine and 25% 2-propanol. The faster eluting compound was **Example 26a**. The slower eluting compound was **Example 26b**.

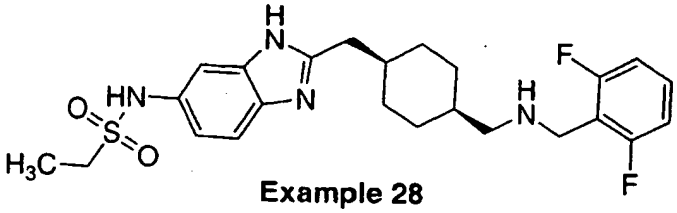
EXAMPLE 27



Example 27

Example 27 was prepared by the following procedure: To a solution of amide (**This does not seem to be an Example above) L-478,227** (200mg, 0.52mmol) in THF (1mL) was added BH_3-THF (1M, 5.0mL). The reaction mixture was heated to 50°C for 12h, cooled and carefully quenched with HCl (1M). The resulting mixture was partitioned between EtOAc/aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, concentrated and purifed by reverse phase HPLC to give **Example 27**: ^{1}H NMR (400MHz, CD_3OD) δ 7.71 (m, 2 H), 7.57 (m, 3 H), 7.18 (t, 2 H); 4.35 (s, 2 H), 3.14 (t, 4 H), 2.21 (m, 1 H), 2.00 (m, 1 H), 1.75-1.40 (m, 8 H) ppm; mass spectrum *m/z* 370 [$(M+H)^+$; calcd for $C_{22}H_{26}F_2N_3$: 370].

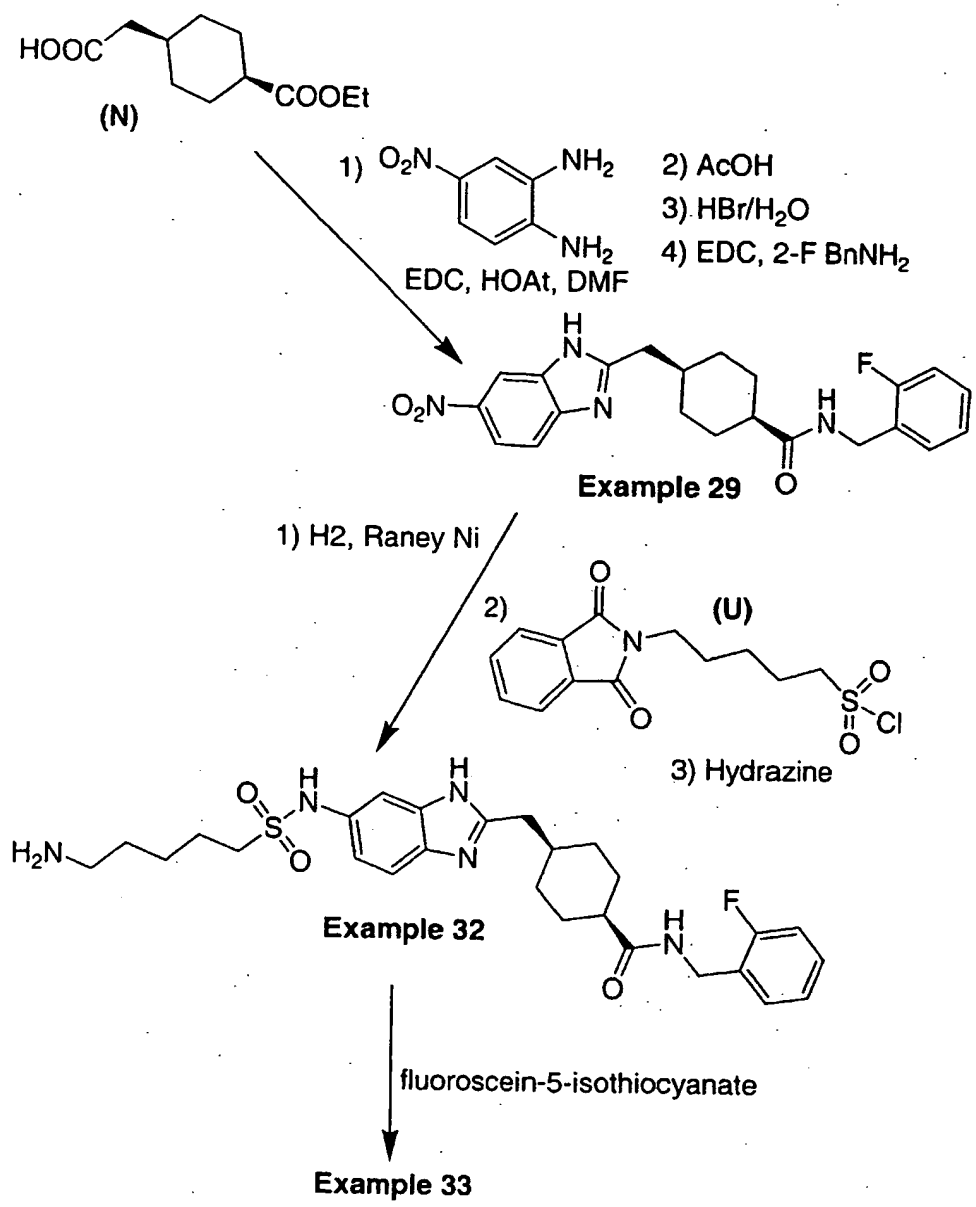
EXAMPLE 28



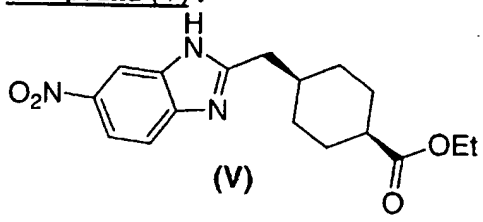
Example 28

Example 28 was prepared by following the above procedure for **Example 27** except acid **Example 19** was used instead of **L-478,227**: mass spectrum *m/z* 477 [$(M+H)^+$; calcd for $C_{24}H_{31}F_2N_4O_2S$: 477].

Compounds of the present invention can be prepared according to **Scheme 11** shown below:


HOOC
COOEt
(N)
1) O_2N NH_2 NH_2
2) AcOH
3) HBr/H_2O
4) EDC, 2-F $BnNH_2$
EDC, HOAt, DMF
Example 29
1) H2, Raney Ni
2)
(U)
3) Hydrazine
H_2N
Example 32
fluoroscein-5-isothiocyanate
Example 33

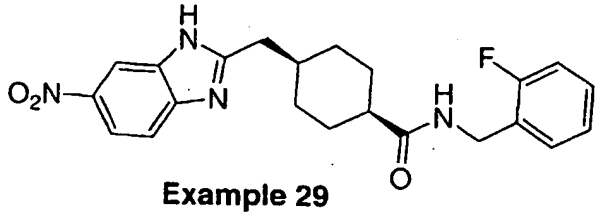
Compound (V) :


O_2N
OEt
(V)

Compound (V) was prepared by the following procedure: To a solution of acid (N) (900mg, 4.2mmol) in DMF (10mL) was added EDC (886mg, 4.6mmol), HOAt (629mg, 4.6mmol) and 4-nitro-1,2-phenylenediamne (643mg, 4.2mmol). The resulting reaction mixture was stirred at room temperature for 16h followed by quenching with aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic layer was washed twice with water, dried over Na_2SO_4, filtered and concentrated.

The resulting crude product was dissolved in acetic acid (5mL) and heated to 130°C for 1.5h. The reaction mixture was cooled, concentrated and partitioned between aqueous $NaHCO_3$ and EtOAc, and the organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was used without purification: mass spectrum *m/z* 332 [$(M+H)^+$; calcd for $C_{17}H_{22}N_3O_4$: 332].

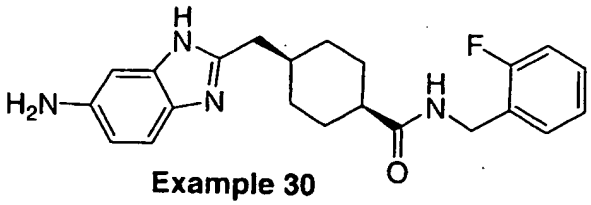
EXAMPLE 29 :



Example 29

Example 29 was prepared by the following procedure: Ester **Compound (V)** (450mg, 1.36mmol) was dissolved in HBr/H_2O (48%, 5mL) and heated to 100°C for 10min. The reaction mixture was cooled, concentrated and the corresponding resulting acid was used without further purification: mass spectrum *m/z* 304 [$(M+H)^+$; calcd for $C_{15}H_{18}N_3O_4$: 304].

To a solution of the above resulting acid (400mg, 1.32mmol), EDC (379mg, 1.98mmol) and HOAt (269mg, 1.98mmol) in anhydrous DMF (5mL) was added 2-fluorobenzylamine (247mg, 1.98mmol) and the resulting reaction mixture was stirred for 2h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc and the organic layer was washed 2x with water. The EtOAc was dried with $MgSO_4$ and concentrate. The crude material was purified by reverse phase HPLC to give **Example 29**: ^1H NMR (300MHz, CD_3OD) δ 8.61 (d, 1 H), 8.42 (dd, 1 H), 7.88 (d, 1 H); 7.24 (m, 2 H), 7.10 (m, 2 H), 4.40 (s, 2 H), 3.10 (d, 2 H), 2.43 (m, 1 H), 2.17 (m, 1 H), 1.90 (m, 3 H), 1.61 (m, 5 H) ppm; mass spectrum *m/z* 411 [$(M+H)^+$; calcd for $C_{22}H_{24}FN_4O_3$: 411].

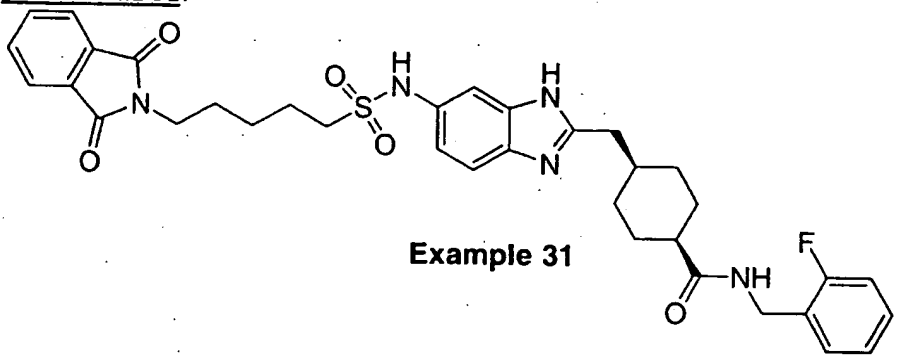


Example 30

EXAMPLE 30

Example 30 was prepared by the following procedure: To a solution of **Example 29** (0.3g, 0.73mmol) in EtOH (4mL) was added 10% Pd/C (0.05g). The resulting reaction mixture was stirred under a balloon of hydrogen. After 2h, the reaction mixture was filtered through celite, concentrated and the crude product purified by reverse phase HPLC to give **Example 30**: mass spectrum *m/z* 381 [$(M+H)^+$; calcd for $C_{22}H_{25}FN_4O$: 381].

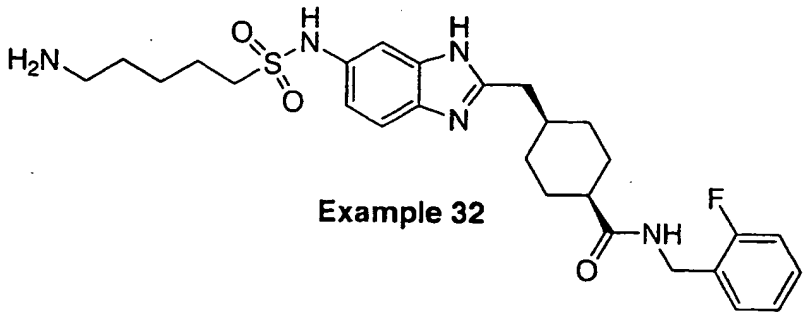
EXAMPLE 31:



Example 31

Example 31 was prepared by the following procedure: To a solution of **Example 30** (15mg, 0.04mmol) in dichloromethane (1mL) was added triethylamine (11μL, 0.08mmol) and sulfonyl chloride **Compound (U)** (12mg, 0.04mmol). The resulting mixture was stirred at room temperature for 30min, concentrated and purified by reverse phase HPLC to give **Example 31**: mass spectrum *m/z* 660 [$(M+H)^+$; calcd for $C_{35}H_{39}FN_5O_5S$: 660].

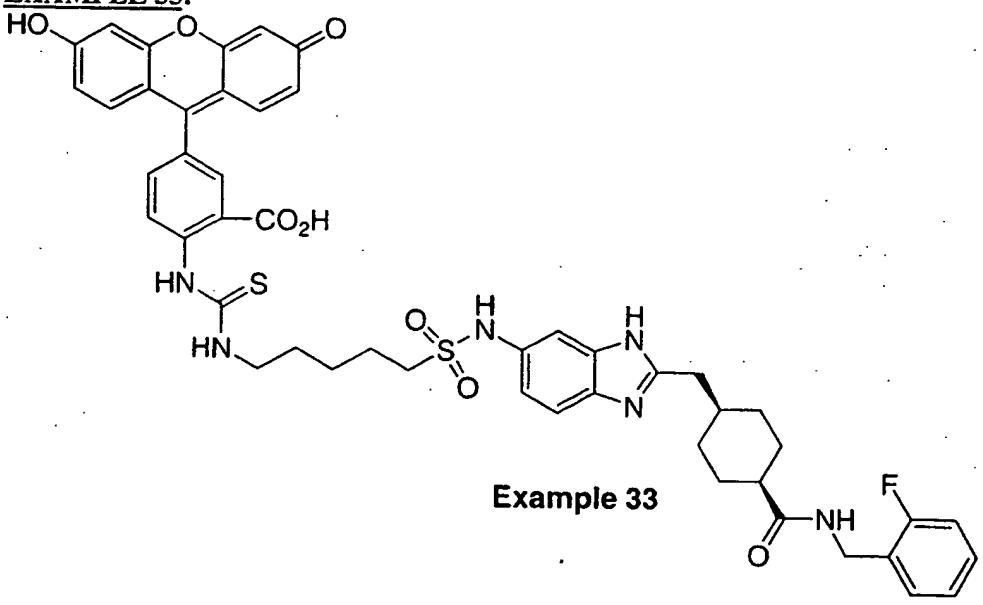
EXAMPLE 32:



Example 32

Example 32 was prepared by the following procedure: To a room temperature solution of **Example 31** (10mg, 0.015mmol) in EtOH (0.5mL) was added hydrazine (4μL, 0.15mmol) and the reaction mixture was stirred for 2h. The reaction mixture was concentrated and purified by reverse phase HPLC to give **Example 32**: mass spectrum *m/z* 530 [$(M+H)^+$; calcd for $C_{27}H_{37}FN_5O_3S$: 530].

EXAMPLE 33:



Example 33

Example 33 was prepared by the following procedure: To a room temperature solution of **Example 32** (8mg, 0.015mmol) in dichloromethane (1mL) and MeOH (0.2mL) was added fluoroscein-5-isothiocyanate (5mg, 0.02mmol) and triethylamine (10μL). The resulting mixture was stirred for 30min, concentrated, and purified by reverse phase HPLC to give **Example 33**: mass spectrum *m/z* 919 [$(M+H)^+$; calcd for $C_{48}H_{48}FN_6O_8S_2$: 919].

Examples 34-106

Examples 34-106 were prepared by procedures similar to those described above.

In Table 1 below, the substituents are shown wherein X_1 corresponds to the NH group of the amide:

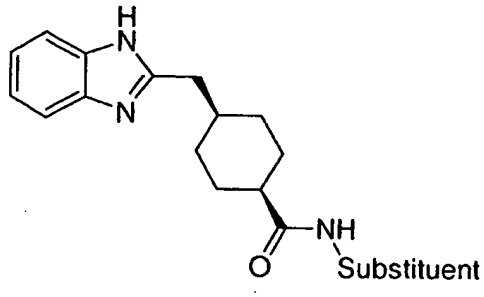
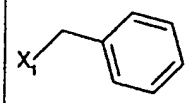
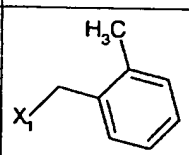
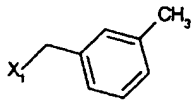
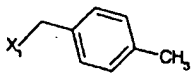
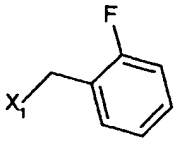
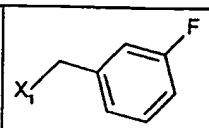
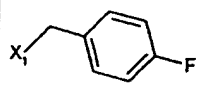
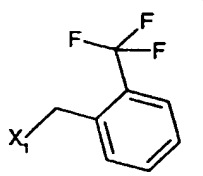
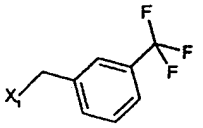
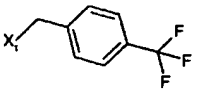
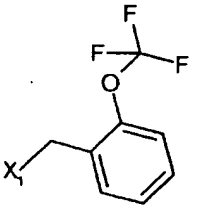
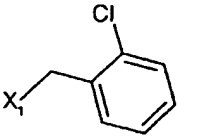
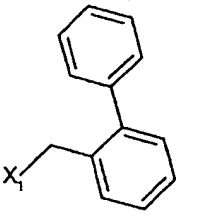
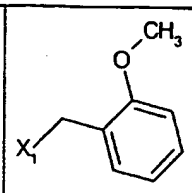
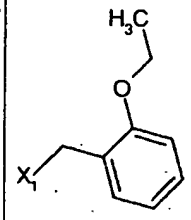
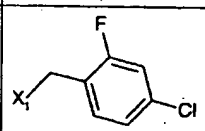
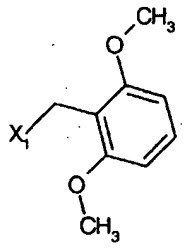
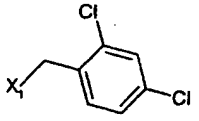
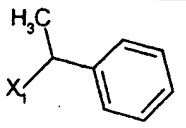
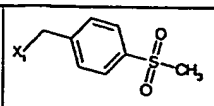
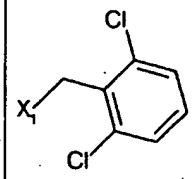
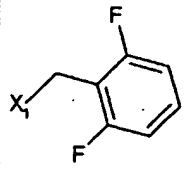


Table 1:

Example	SUBSTITUENT	MS	NAME
34		348	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
35		362	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-methyl-benzylamide
36		362	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-methyl-benzylamide
37		362	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-methyl-benzylamide
38		366	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide

39		366	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-fluoro-benzylamide
40		366	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-fluoro-benzylamide
41		416	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide
42		416	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-trifluoromethyl-benzylamide
43		416	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-trifluoromethyl-benzylamide
44		432	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-trifluoromethoxy-benzylamide
45		382	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-chloro-benzylamide
46		424	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-phenyl-benzylamide

47		378	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
48		392	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-ethoxy-benzylamide
49		400	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-4chloro-benzylamide
50		408	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,6-dimethoxy-benzylamide
51		417	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,4-dichloro-benzylamide
52		362	cis-4-(1H-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid (1-phenyl-ethyl)-amide

53		426	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-methanesulfonyl-benzylamide
54		417	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,6-dichloro-benzylamide
55		384	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,6-difluoro-benzylamide

In Table 2 below, the substituents are shown wherein X_1 corresponds to the NH group of the amide:

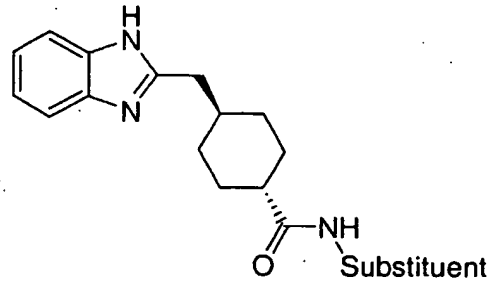
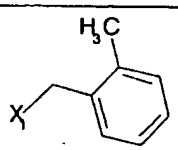
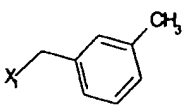
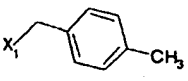
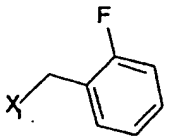
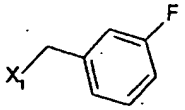
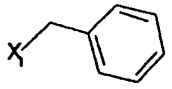
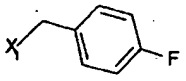
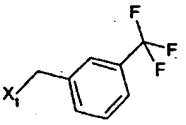
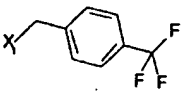


Table 2:

Example	SUBSTITUENT	MASS	NAME
56		362	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-methyl-benzylamide
57		362	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-methyl-benzylamide
58		362	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-methyl-benzylamide

59		366	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide
60		366	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-fluoro-benzylamide
61		348	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
62		366	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-fluoro-benzylamide
63		416	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide
64		416	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-trifluoromethyl-benzylamide
65		416	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-trifluoromethyl-benzylamide

In Table 3 below, the substituents are shown wherein X_1 corresponds to the NH group of the amide:

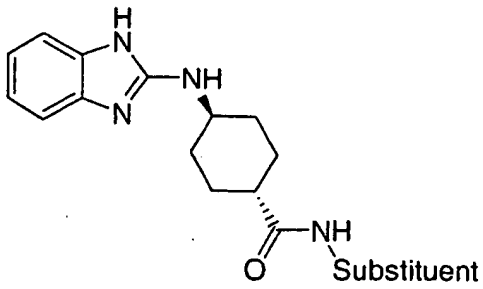
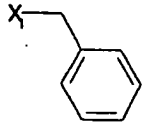
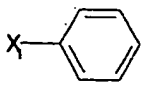
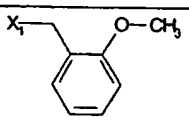
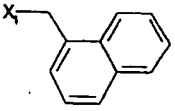
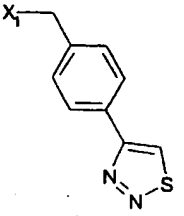
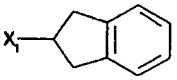
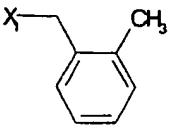
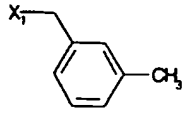
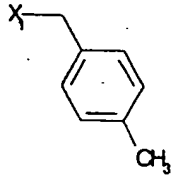
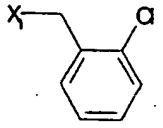
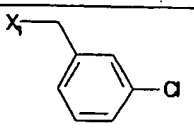
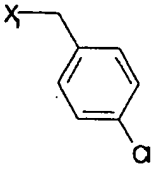
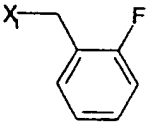
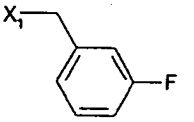
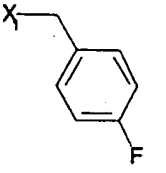
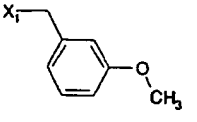
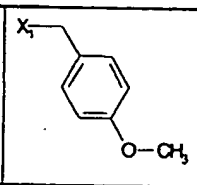
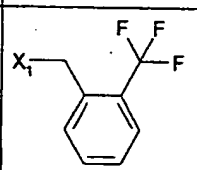
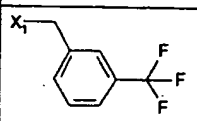
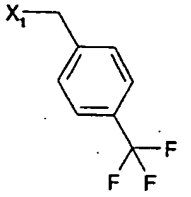
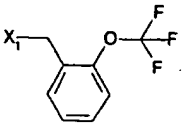
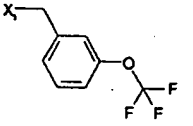
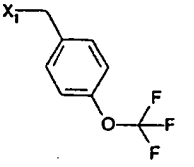
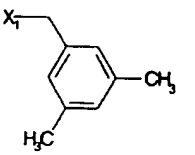
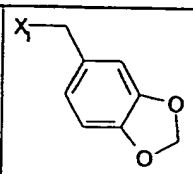
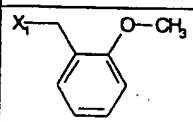
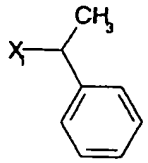
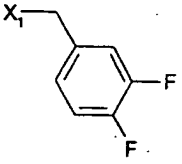
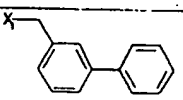


Table 3:

Example	SUBSTITUENT	MS	NAME
66		349	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide
67		335	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid phenylamide
68		379	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
69		399	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (naphthalen-1-ylmethyl)-amide
70		433	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-(1,2,3)thiadiazol-4-yl-benzylamide.
71		375	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid indan-2-ylamide
72		363	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methyl-benzylamide

73		363	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-methyl-benzylamide
74		363	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-methyl-benzylamide
75		383	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-chloro-benzylamide
76		383	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-chloro-benzylamide
77		383	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-chloro-benzylamide
78		367	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-fluoro-benzylamide
79		367	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-fluoro-benzylamide
80		367	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-fluoro-benzylamide
81		379	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-methoxy-benzylamide

82		379	trans-4-(1*H*-Benzolmidazol-2-ylamino)-cyclohexanecarboxyilic acid 4-methoxy-benzylamide
83		417	trans-4-(1*H*-Benzolmidazol-2-ylamino)-cyclohexanecarboxyilic acid 2-trifluoromethyl-benzylamide
84		417	trans-4-(1*H*-Benzolmidazol-2-ylamino)-cyclohexanecarboxyilic acid 3-trifluoromethyl-benzylamide
85		417	trans-4-(1*H*-Benzolmidazol-2-ylamino)-cyclohexanecarboxyilic acid 4-trifluoromethyl-benzylamide
86		433	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxyilic acid 2-trifluoromethoxy-benzylamide
87		433	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxyilic acid 3-trifluoromethoxy-benzylamide
88		433	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxyilic acid 4-trifluoromethoxy-benzylamide
89		377	trans-4-(1*H*-Benzolmidazol-2-ylamino)-cyclohexanecarboxyilic acid 3,5-dimethyl-benzylamide

90		393	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (benzo(1,3)dioxol-5-ylmethyl)-amide
91		379	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
92		363	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (1-phenyl-ethyl)-amide
93		363	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid phenethyl-amide
94		385	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3,4-difluoro-benzylamide
95		425	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-phenyl-benzylamide

In Table 4 below, the substituents are shown wherein X_1 corresponds to the NH group of the amide:

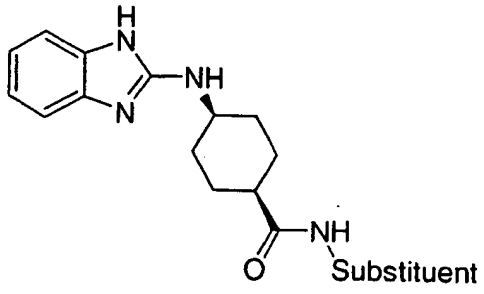
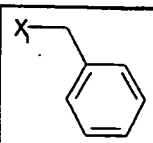
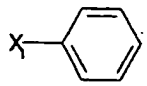
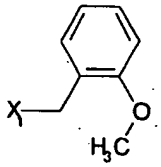
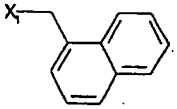
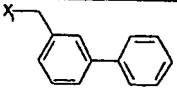
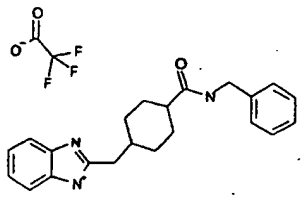
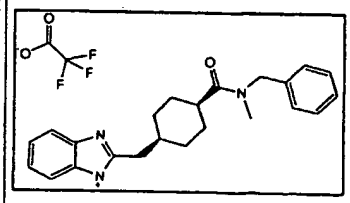
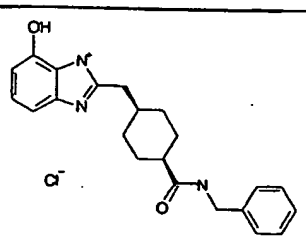
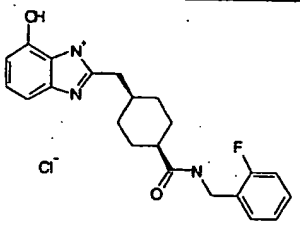
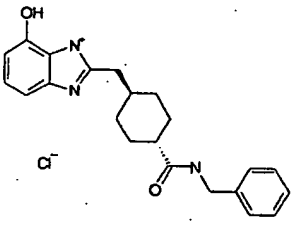
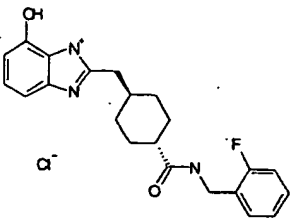


Table 4:

96		349	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide
97		335	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid phenylamide
98		379	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
99		399	cis-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (naphthalen-1-ylmethyl)-amide
100		425	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-phenyl-benzylamide

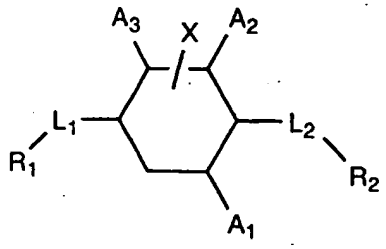
Examples 102-106:

Example	Structure	MASS	NAME
101		348	4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
102		362	4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzyl-methyl-amide

103		364	cis-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
104		382	cis-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide
105		364	trans-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
106		382	trans-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_1 is 2-benzimidazole, 2-imidazopyridine, or 2-quinazoline; optionally substituted with fluoro, amino, or hydroxy;

R_2 is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

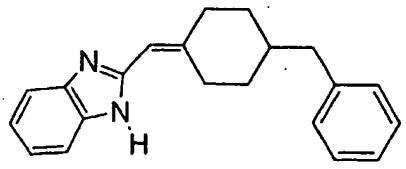
L_1 and L_2 are independently C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, amino, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

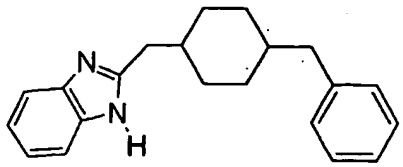
A_1, A_2, and A_3 are each hydrogen or i) A_1 and A_2 form a two carbon bridge or ii) A_1 and A_3 form a two carbon bridge; and

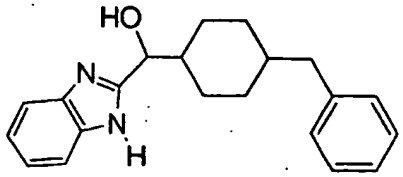
optionally substituted with X, wherein X is hydroxy, amino, C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

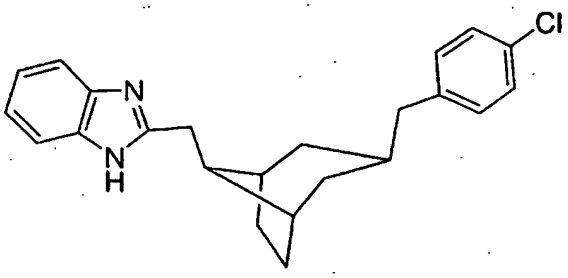
2. The compound according to claim 1, wherein R_1 is 2-benzimidazole.

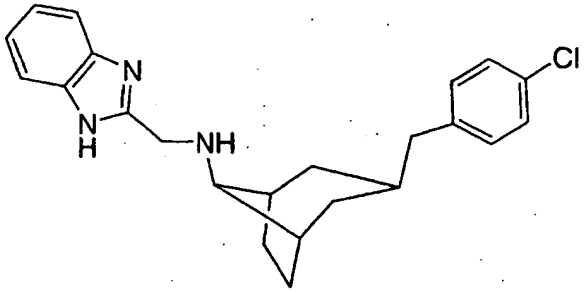
3. The compound according to claim 1, wherein said compound is

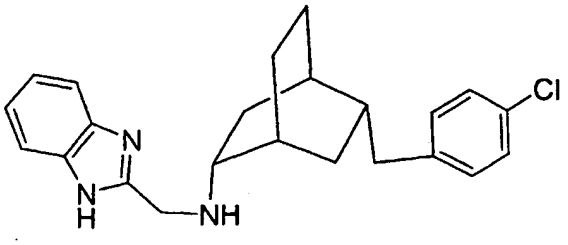


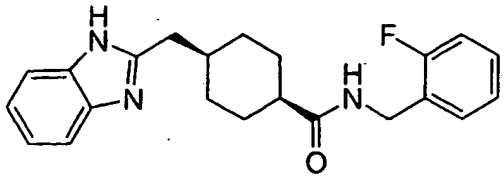


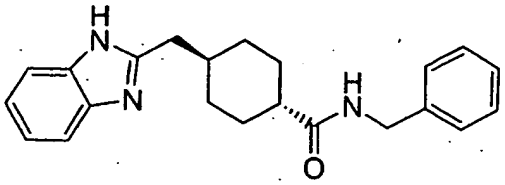


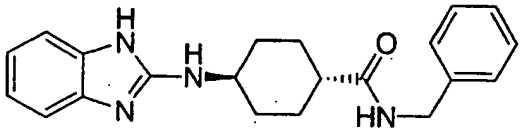


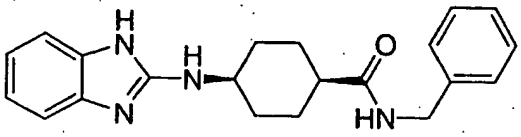


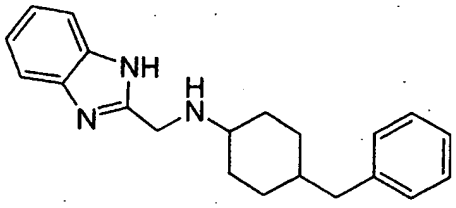


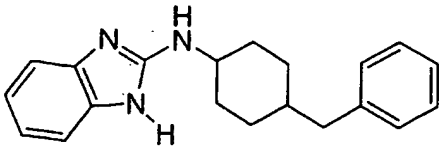










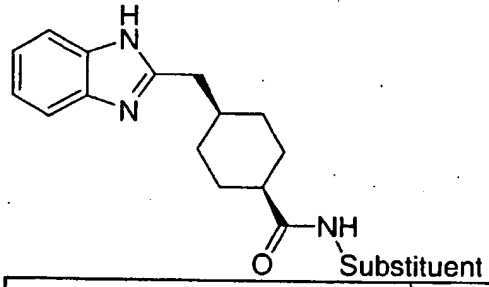


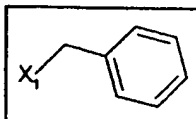
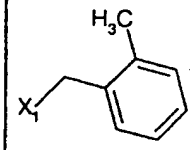
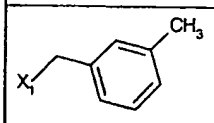
or a pharmaceutically acceptable salt thereof.

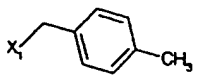
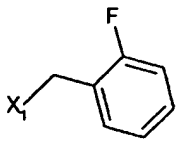
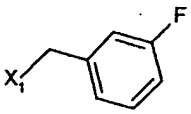
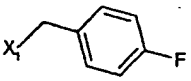
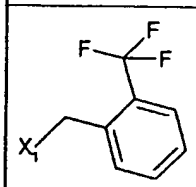
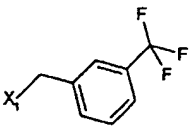
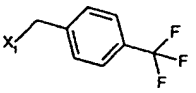
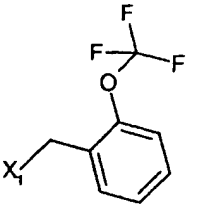
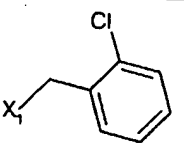
4. The compound according to claim 1, wherein said compound is

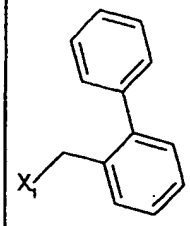
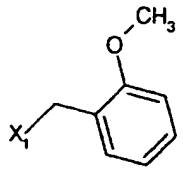
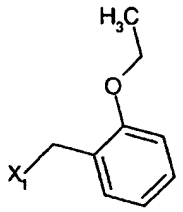
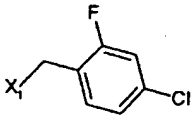
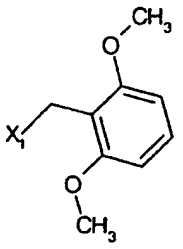
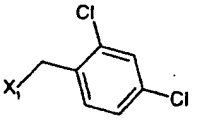
2-(4-Benzyl-cyclohexylidenemethyl)-1H-benzimidazole;
2-(4-Benzyl-cyclohexylmethyl)-1H-benzimidazole;
(1H-Benzoimidazol-2-yl)-(4-benzyl-cyclohexyl)-methanol;
2-[3-(4-Chloro-benzyl)-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;
(1H-Benzimidazol-2-ylmethyl)-[3-(4-chloro-benzyl)-bicyclo[3.2.1]oct-8-yl]-amine;
(1H-Benzimidazol-2-ylmethyl)-[5-(4-chloro-benzyl)-bicyclo[2.2.2]oct-2-yl]-amine;
Cis-4-(1*H*-benzimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide;
Trans-4-(1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide;
Trans-4-(1*H*-benzimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide;
Cis-4-(1*H*-benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide;
(1H-Benzimidazol-2-ylmethyl)-(4-benzyl-cyclohexyl)-amine;
(1H-Benzimidazol-2-yl)-(4-benzyl-cyclohexyl)-amine; or
a pharmaceutically acceptable salt thereof.

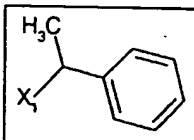
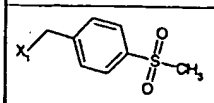
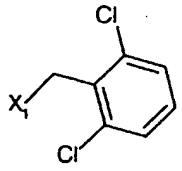
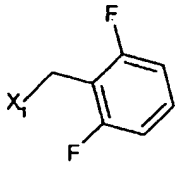
5. The compound according to claim 1, wherein said compound is selected from the table below wherein X_1 corresponds to the NH group of the amide:



Substituent	
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-methyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-methyl-benzylamide

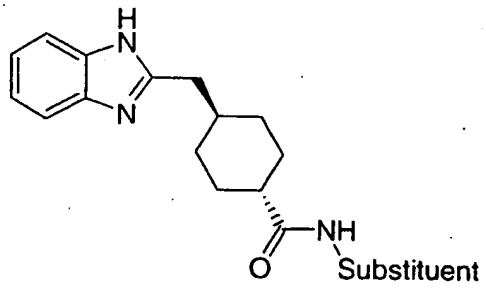
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-methyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-fluoro-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-fluoro-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-trifluoromethyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-trifluoromethyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-trifluoromethoxy-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-chloro-benzylamide

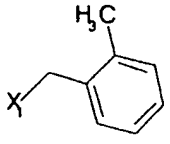
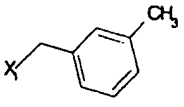
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-phenyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-ethoxy-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-4chloro-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,6-dimethoxy-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,4-dichloro-benzylamide

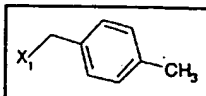
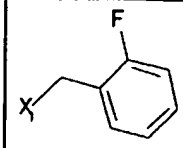
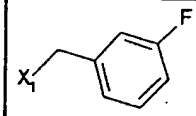
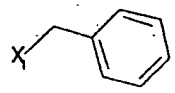
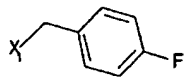
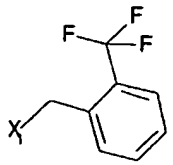
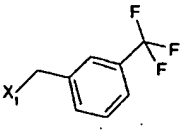
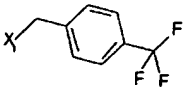
	cis-4-(1H-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid (1-phenyl-ethyl)-amide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-methanesulfonyl-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,6-dichloro-benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2,6-difluoro-benzylamide

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein said compound is selected from the table below wherein X_1 corresponds to the NH group of the amide:

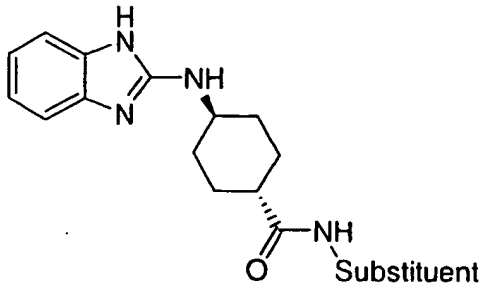


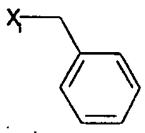
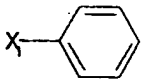
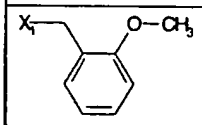
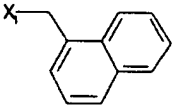
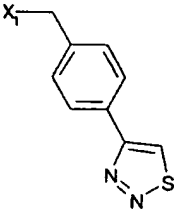
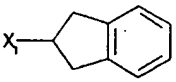
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-methyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-methyl-benzylamide

	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-methyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-fluoro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-fluoro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 3-trifluoromethyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 4-trifluoromethyl-benzylamide

or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein said compound is selected from the table below wherein X_1 corresponds to the NH group of the amide:



	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxyilic acid benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxyilic acid phenylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxyilic acid 2-methoxy-benzylamide
	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (naphthalen-1-ylmethyl)-amide
	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-(1,2,3)thiadiazol-4-yl-benzylamide
	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid Indan-2-ylamide

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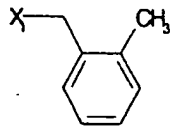
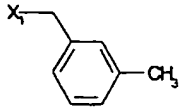
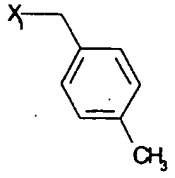
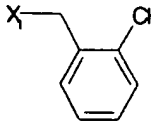
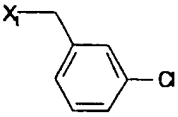
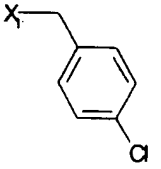
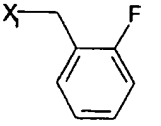
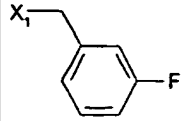
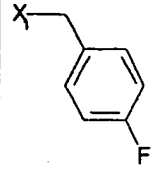
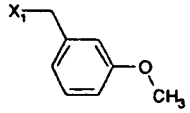
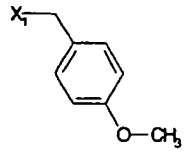
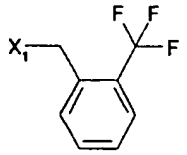
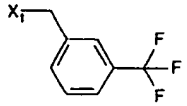
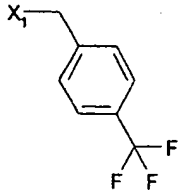
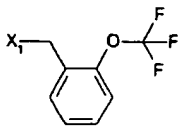
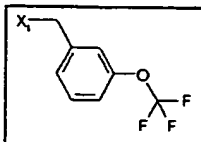
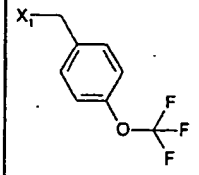
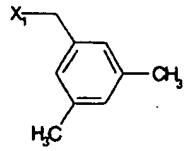
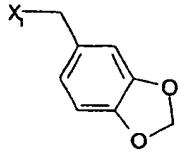
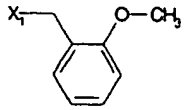
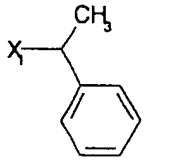
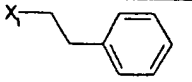
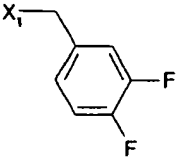
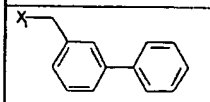
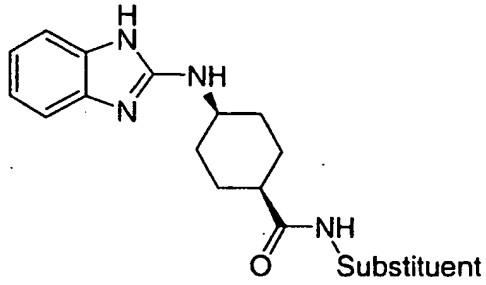
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-methyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-methyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-chloro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-chloro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-chloro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-fluoro-benzylamide

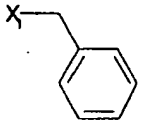
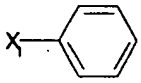
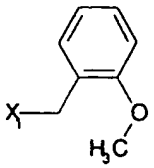
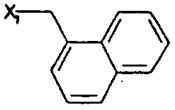
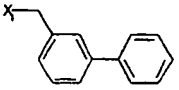
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-fluoro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-fluoro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-methoxy-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-methoxy-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-trifluoromethyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-trifluoromethyl-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-trifluoromethoxy-benzylamide

	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-trifluoromethoxy-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 4-trifluoromethoxy-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3,5-dimethyl-benzylamide
	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (benzo(1,3)dioxol-5-ylmethyl)-amide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (1-phenyl-ethyl)-amide
	trans-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid phenethyl-amide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3,4-difluoro-benzylamide
	trans-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-phenyl-benzylamide

or a pharmaceutically acceptable salt thereof.

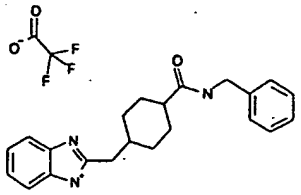
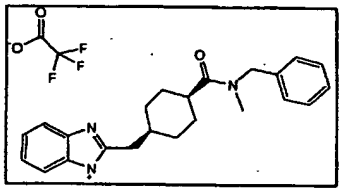
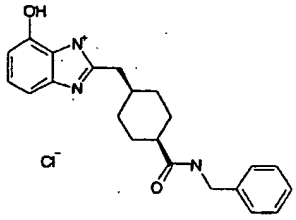
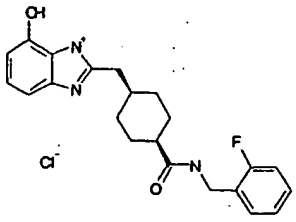
8. The compound according to claim 1, wherein said compound is selected from the table below wherein X_1 corresponds to the NH group of the amide:

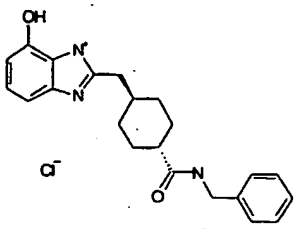
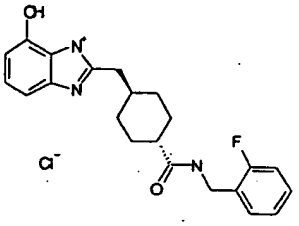


	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzylamide
	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid phenylamide
	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 2-methoxy-benzylamide
	cis-4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid (naphthalen-1-ylmethyl)-amide
	cis-4-(1*H*-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid 3-phenyl-benzylamide

or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, wherein said compound is selected from the table below

	4-(1*H*-Benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
	4-(1H-Benzoimidazol-2-ylamino)-cyclohexanecarboxylic acid benzyl-methyl-amide
	cis-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid benzylamide
	cis-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxylic acid 2-fluoro-benzylamide

	trans-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxyilic acid benzylamide
	trans-4-(3-Hydroxy-1*H*-benzoimidazol-2-ylmethyl)-cyclohexanecarboxyilic acid 2-fluoro-benzylamide

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising an inert carrier and an effective amount of a compound according to claim 1.

11. The pharmaceutical composition according to claim 10 useful for the treatment of pain.

12. The pharmaceutical composition according to claim 10 useful for the treatment of migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke.

13. A method of treating pain comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 1.

14. A method of treating migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/29928

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 249/16; A61K 31/415
US CL : 548/257; 514/394

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/257; 514/394

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Database, East West

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,820,757 A (SPANG et al.) 11 April 1989, col. 9, lines 5-10.	NONE

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 DECEMBER 2000	Date of mailing of the international search report 25 JAN 2001
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Form PCT/ISA/210 (second sheet) (July 1998) *